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ANNALS OF THE RHEUMATIC DISEASES

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LONDON
BRITISH MEDICAL ASSOCIATION
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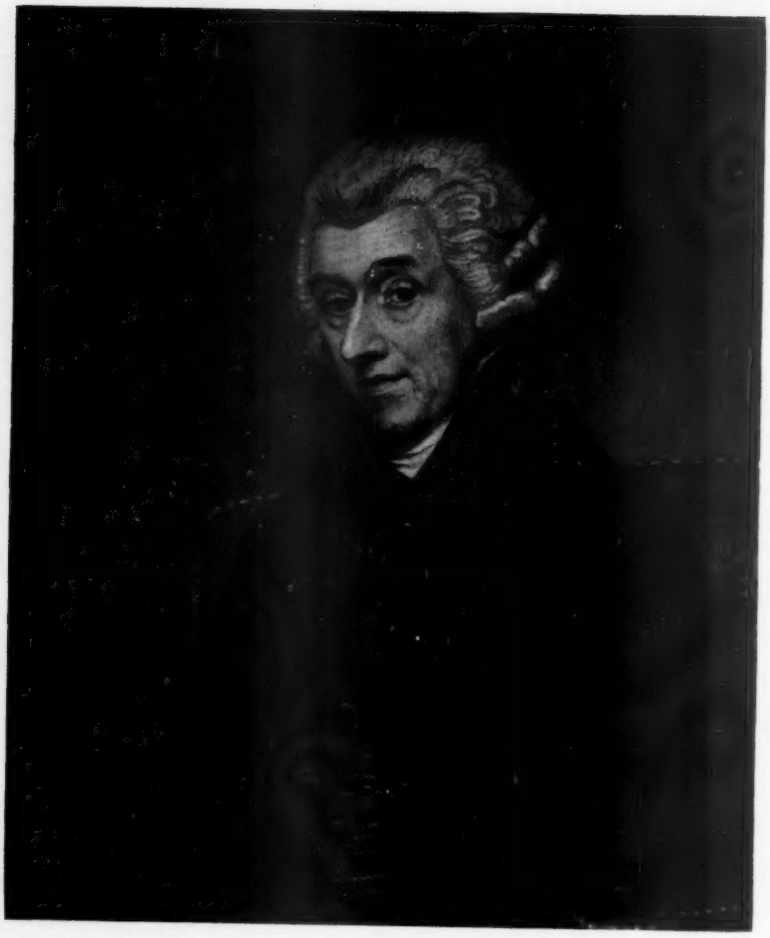


W. Heberden

[Frontispiece

HEBERDEN SOCIETY

DOCTOR WILLIAM HEBERDEN*

BY

DOUGLAS GUTHRIE

Edinburgh

The tall and spare, yet stately, figure of Dr. William Heberden must have been a familiar sight to many Londoners of the 18th century. That period was rich in great physicians, and in London the leading practitioners were at first Radcliffe and Mead, to be followed by Fothergill, Lettsom, Baillie, and Heberden. Heberden was second to none, and although he held no hospital appointment and made no discovery, his contribution to medical progress was considerable. Samuel Johnson, who was his patient, called him the last of the great physicians, *ultimus Romanorum*, although he might be regarded more correctly as the first of the modern physicians, so fresh and unbiassed was his outlook.

At that time London was the centre of practice, just as Edinburgh was the centre of teaching. Heberden was still a student at Cambridge when in 1728 Alexander Monro returned from Leyden to found the Edinburgh Medical School. Born in 1710, William Heberden died in 1801, and thus his long life-span almost coincided with the 18th century. Our knowledge of his domestic life is scanty. He was born at Southwark, the son of Richard Heberden, and was educated at the grammar school of St. Saviour, and from 1724 at Cambridge, where he became a fellow of St. John's College in 1731. For ten years after graduating M.D. in 1739 he practised in Cambridge, and taught *materia medica*†; then he removed to London, where for many years he conducted a large and fashionable practice, living first at Cecil Street, Strand, and later at 79 Pall Mall, with a country residence at Datchet, near Windsor. He was twice married, and had seven sons and three daughters from whom a succession of physicians and clergymen is descended, but the only member of his family to survive him was a son of the second marriage, usually known as William Heberden the Younger.

Our patron retired at the comparatively early age of 72, and such, in brief, is his biography, so far as it is known. That he was a classical scholar of distinction is evident from the fact that he edited some of the plays of Euripides. He had many friends in the field of literature, some of whom were his patients. Dr. Johnson we have already mentioned; George Crabbe described him as " tender, ardent, and kind ", and the poet Cowper wrote of him:

> Virtuous and faithful Heberden, whose skill
> Attempts no task it cannot well fulfil.

Among his friends was a certain Dr. Conyers Middleton, who had composed

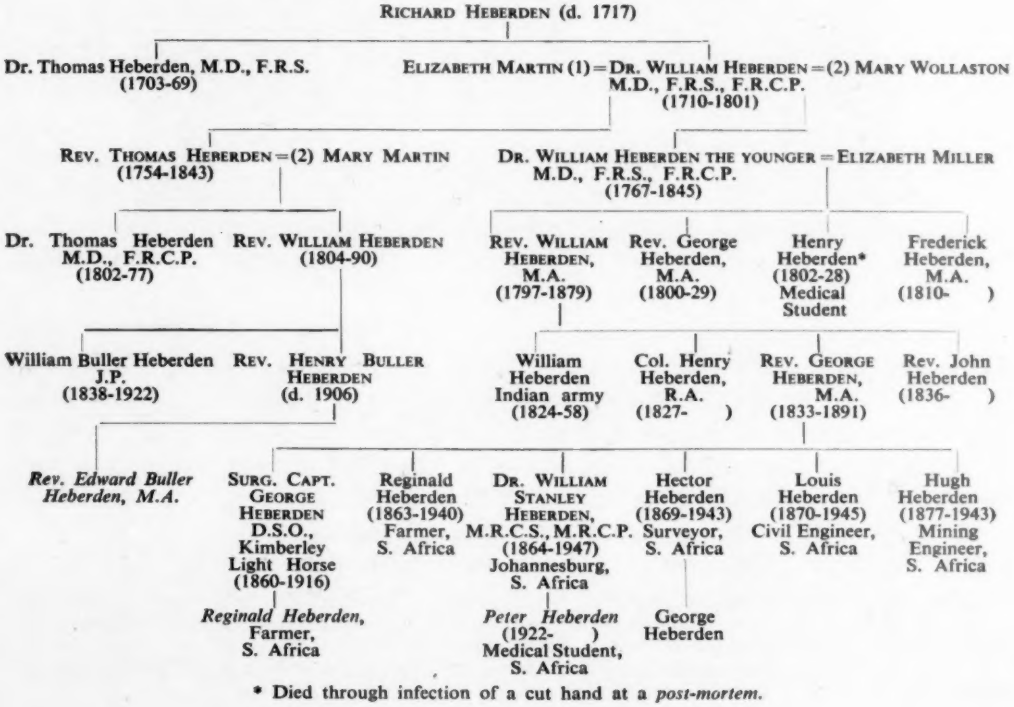
* Read before the Heberden Society in Edinburgh on May 10, 1951.

† The cabinet of *materia medica* used by Heberden in teaching that subject is still preserved in the Library of St. John's College, Cambridge.

an unorthodox work entitled " The Inefficiency of Prayer " which was left unpublished at his death. When the widow consulted Heberden regarding its publication, he found a publisher who offered £150 for the manuscript; thereupon Heberden sent a cheque for £200 to the widow and consigned the work to the fire, since he considered that, if published, it would be injurious to the memory of the writer. The action was characteristic of the man, and he deserves to be remembered not only for his learning, but for those qualities of modesty, sympathy, and kindness which he possessed in full measure.

Heberden's earliest published work was a tract written in 1745, while he was still teaching at Cambridge, entitled " Antitheriaca; An Essay on Mithradatium and Theriaca ", pointing out the uselessness of those remedies. The poison antidote used by Mithradates, king of Pontus (who died in 63 B.C.), consisted of 20 leaves of rue, 1 grain of salt, and 2 dried figs. Celsus (A.D. 30) mentions 38 ingredients. Nero's physician, Andromachus, added viper's flesh to the remedy and called it Theriac. The Theriac of the Pharmacopoeia of the Royal College of Physicians of London, dated 1724, contains 62 ingredients, but in spite of Dr. Heberden's exposure it remained an official remedy until 1788. In 1752, shortly after his removal to London, Heberden was admitted a Fellow of the Royal Society, and contributed four papers to the *Philosophical Transactions*: " On the Effects of Lightning ", " On Rain-gauges ", " On Salt found in Teneriffe ", and " An Account of a very large Calculus ".

SELECT TABLE OF THE HEBERDEN FAMILY


RICHARD HEBERDEN (d. 1717)
Dr. Thomas Heberden, M.D., F.R.S. (1703-69)
ELIZABETH MARTIN (1) = DR. WILLIAM HEBERDEN = (2) MARY WOLLASTON
M.D., F.R.S., F.R.C.P. (1710-1801)
REV. THOMAS HEBERDEN = (2) MARY MARTIN (1754-1843)
DR. WILLIAM HEBERDEN THE YOUNGER = ELIZABETH MILLER
M.D., F.R.S., F.R.C.P. (1767-1845)
Dr. Thomas Heberden M.D., F.R.C.P. (1802-77)
REV. WILLIAM HEBERDEN (1804-90)
REV. WILLIAM HEBERDEN, M.A. (1797-1879)
Rev. George Heberden, M.A. (1800-29)
Henry Heberden* (1802-28) Medical Student
Frederick Heberden, M.A. (1810-)
William Buller Heberden J.P. (1838-1922)
REV. HENRY BULLER HEBERDEN (d. 1906)
William Heberden Indian army (1824-58)
Col. Henry Heberden, R.A. (1827-)
REV. GEORGE HEBERDEN, M.A. (1833-1891)
Rev. John Heberden (1836-)
Rev. Edward Buller Heberden, M.A.
SURG. CAPT. GEORGE HEBERDEN D.S.O., Kimberley Light Horse (1860-1916)
Reginald Heberden (1863-1940) Farmer, S. Africa
DR. WILLIAM STANLEY HEBERDEN, M.R.C.S., M.R.C.P. (1864-1947) Johannesburg, S. Africa
Hector Heberden (1869-1943) Surveyor, S. Africa
Louis Heberden (1870-1945) Civil Engineer, S. Africa
Hugh Heberden (1877-1943) Mining Engineer, S. Africa
Reginald Heberden, Farmer, S. Africa
Peter Heberden (1922-) Medical Student, S. Africa
George Heberden

* Died through infection of a cut hand at a *post-mortem*.

For the *Medical Transactions* of the Royal College of Physicians he wrote other papers, of which " Observations Upon the Ascarides ", " Of Night-Blindness or Nyctalopia ", " Of the Diseases of the Liver ", " Remarks on the Pulse ", and " Account of the Noxious Effects of Some Fungi " are only a few.

Throughout his many years of practice, William Heberden was in the habit of making notes " relating to the nature and cure of disease ", and of transcribing and arranging them at the end of every month. In this manner he collected a vast mass of material, written in Latin and English, and from it compiled, in 1782, his " Commentaries on the History and Cure of Diseases ", which he entrusted to the care of his son, to be published after his death. The book appeared in 1802, and remains to this day one of the most useful and readable of medical classics. In it are described the *Digitorum Nodi* which we call " Heberden's Nodes ", little hard knobs, frequently seen upon the finger, and continuing for life. Even more worthy of mention is Heberden's classic description of " Pectoris Dolor ":

> a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare. The seat of it, the sense of strangling, and the anxiety with which it is attended, may make it not unproperly be called *angina pectoris*.

The disease had already been described in 1632 by the Earl of Clarendon, who spoke then of the death of his father:

> the pain in his arm seizing upon him, he fell down dead, without the least motion of any limb.

Naturally, we wish to know what Heberden has to say of Rheumatism, which he defines as " a common name for many aches and pains, which have yet no peculiar appellation, though owing to very different causes ". He describes two varieties, " acute and chronical ", telling us that " both kinds attack indiscriminately males and females, rich and poor ".

Heberden's description of " chicken pox " was opportune, at a time when it was often confused with small pox. Edward Jenner's discovery of vaccination in 1796 had not yet met with general adoption. At that time, too, malaria was still prevalent in England. Heberden shows that the quartan fever is more serious than the tertian, and more resistant to treatment by Peruvian bark. Another topical description deals with " malignant sore throat ", which occurred in epidemic form and was described in 1748 by Fothergill. Heberden regarded it as a form of scarlet fever, remarking that " both are names for the same disorder, and both are epidemical at the same time ". One of the longest and most interesting chapters deals with jaundice, and the shortest dismisses hernia in a single sentence:

> Ruptures require no other remedy than a truss.

But no extracts from the Commentaries can be adequate; the clinical pictures, clear and concise, must be studied and pondered. It is not surprising that the book had an enormous popularity although good copies are now rare.

The portrait of Heberden here reproduced* hangs in the Royal College of

* The reproduction, from an engraving by J. Thomson, is included in T. J. Pettigrew's *Biographical Memoirs* (1839).

Physicians. Sir William Beechey, R.A., a famous artist of the day, went down to Windsor in 1796 to paint it, but he forgot his canvas, and it is said that he painted it on one of his subject's shirts !

Heberden's son, William Heberden the Younger (1767-1845), was also a distinguished physician, although his fame, as so often happens, was overshadowed by his father's achievement. He lived to the age of 78, but retired early from practice and devoted his attention to theology and to the education of his nine children. Nevertheless, he attained eminence sufficient to warrant his appointment as Physician to St. George's Hospital in 1793, and to King George III in 1809. The King's illness dragged on for years, with Matthew Baillie and Heberden in attendance, and Francis Willis as mental consultant, a collaboration recorded by a contemporary in this doggerel:

> The King employs the doctors daily—
> Willis, Heberden and Baillie;
> All extremely clever men—
> Baillie, Willis, Heberden,
> But doubtful which most sure to kill is—
> Baillie, Heberden, or Willis.

He published " Observations on the Increase and Decrease of different Diseases " (1801), and " Morborum puerilium epitome " (1804), Eng. trans., (1805), both interesting and useful works.

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PRESIDENTIAL ADDRESS, APRIL 6, 1951

THE DIAGNOSTIC SIGNIFICANCE OF PAIN

BY

SIR HENRY COHEN

In choosing my subject for this address I have been influenced not only by the many recent advances in our knowledge of the mechanisms of pain, which are not yet woven into the fabric of clinical medicine, but also by my experience in both teaching and practice which leads me to believe that there is a diminishing appreciation in these days of high-powered diagnostic instruments, of the help which a careful analysis of pain, the most common presenting symptom of disease, can give in diagnosis. And this is of special significance and importance in the " rheumatic diseases ", where words and names have too readily displaced understanding; if this be doubted I shall sustain my thesis by a brief historical note.

Hippocrates used the term " arthritis " for joint diseases, but the name " rheumatism " was introduced by Galen 1,800 years ago. It derived from the then prevalent humoral pathology and was intended to indicate that the disease arose from a flow of peccant humors (Latin, *rheuma*, a flux). Hence all diseases thought to be due to such a discharge were labelled " rheumatic ", and this term was applied not only to diseases of joints but also to diseases of serous membranes, e.g. rheumatic pleurisy, and to surface discharges, e.g. rheumatic catarrh. It was these " drops " of fluid into the joints and tissues which gave us the name " gout " (Latin, *gutta*, a drop). It is to Sydenham that we owe the conception of diseases as specific entities, a reversion in essence to the ancient demoniacal conception of disease. For Sydenham, diseases were " to be reduced to certain and determinate kinds, with the same exactness as we see it done by botanic writers in their treatises of plants ", and they were held to possess " certain distinguishing signs which nature has particularly affixed to every species ". As a natural historian of disease, Sydenham recognized the constantly recurring patterns in the clinical pictures of acute rheumatism, of chorea, and of gout. Gradually the causes of many forms of arthritis were unmasked and the term " rheumatism " began to be used only for those painful diseases of the locomotor system—of joints, muscles and tendons, bursae, fascia, and bony skeleton—for which no specific and necessary causes could be found. Although the pain, swelling, and limited mobility of joints in arthritis left little doubt about the site of disease, in the so-called " non-articular " rheumatic states, a host of names was introduced, such as fibrositis, fasciomyositis, panniculitis, neuritis, etc., of which it could in truth be said that usually they simply

masked ignorance of the cause of the painful malady from which a patient was suffering. No anatomical change, no functional or metabolic disturbance, and no pathology was customarily observed, though many hypotheses were formulated. Hence it is that, if we are not to " surrender judgment to the fascination of a name ", we must as physicians take heed of, and not simply pay lip service to, Hilton's injunction that " every pain has its distinct and pregnant signification if we will but carefully search for it ".

The first point to be stressed is that pain is a *percept*; it is subjective and we are, therefore, largely dependent on the patient's description of his pain for its interpretation. He must be a good witness and we must patiently pursue our task of exploring its site and radiation, its quality, its intensity, and the various modifications and alterations of bodily activity or external environment which excite, aggravate, or alleviate it. Since it is a percept, both the strength of the stimulus giving rise to pain, and the sensitivity of the central receptor mechanism on which nerve impulses impinge, will determine its intensity. Stick a pin in one patient and he says stolidly, " It's a prick "; but another will scream and withdraw violently. So we cannot judge the intensity of pain by the patient's reaction to it. Indeed, all objective signs which accompany pain give equivocal responses, so that little fruitful work on this subject has emerged from laboratory animal experiments. Only in man is the investigation of pain likely to yield useful data, though their interpretation may well be difficult.

For pain, as for all sensations, we can, without entering into the philosophical implications of Cartesian dualism, recognize two stages in perception. The first is anatomical: a noxious stimulus to pain receptors in the various tissues or organs of the body gives rise to an impulse which traverses a pathway through the peripheral nerve or sympathetic chains to spinal root ganglia; from there it passes to a cell station in the posterior horns, and thence through the anterior commissure to the opposite antero-lateral (spino-thalamic) tract, along which it ascends through the brain stem to the thalamus; its cortical associations are not yet clearly defined. When it reaches its cell stations in the brain, electrical and biochemical changes take place, but these are not pain. In some way, which remains obscure, there occurs at this stage in the normal, sentient, conscious being, an awareness of pain in a particular location which has its special quality and intensity.

The anatomical chain plays an important part in determining where pain is felt and also its quality. If we apply a noxious stimulus to any part of a nerve trunk containing pain fibres, pain will be referred to the area of distribution of the peripheral receptors of that nerve; for example, whether we faradize the ulnar nerve at the elbow or in the axilla, pain will be localized to the little finger and adjacent half of the ring finger; and if a prolapsed intervertebral disk irritates the left 4th lumbar root, pain will be felt down the left leg in the area of the peripheral distribution of this root. Like all root pains this distribution is segmental.

But there are other pains of segmental distribution which for us are of greater import. Briefly these arise from deep structures—muscles and bones, deep joints, and viscera. All these deep tissues and organs receive their sensory nerve supply

from certain segments of the spinal cord, e.g. the stomach from T_7-T_9, the small intestine from T_9-T_{11}, and so forth. Disease in these deep structures gives rise to pain vaguely localized in the same segments at varying depths from the surface, and commonly in only part of the segment; hence cardiac disease may give pain in the arm (from T_1), diaphragmatic disease in the shoulder (from C_4), kidney disease in the lower abdomen and groin (from T_{10}-L_1). I have dealt with the probable mechanism of this segmental distribution of pain in my Lettsomian Lectures (Cohen, 1948a). Segmental pain of this type may arise in an intervertebral disk lesion from disease of the disk itself, and can easily be differentiated from that component of the pain in a prolapsed disk which is due to irritation of the emerging spinal nerve; intervertebral arthritis, inflammatory lesions, strains and tears of muscles and tendons give rise to similar segmental pain, not involving the whole segment if mild, but becoming more widespread in its segmental distribution in its more intense forms.

Thus pains of the same segmental distribution may arise from disease of any structure—muscle, joint, periosteum, bone, or viscus—which is innervated from this segment, and its localization alone will not decide which segmental structure is diseased. This, as we shall shortly discuss, is disclosed by ascertaining what factors excite, aggravate, or alleviate the pain.

Before proceeding with this, however, I would remind you that although patients use a variety of adjectives to describe the quality of their pain, such as burning, aching, stabbing, tearing, throbbing, lightning, stitch-like, etc., there are essentially two main qualities of pain though intermediate varieties may be found.

The first or *superficial* pain is pricking, or if prolonged, burning; it is accurately localized and causes but little systemic disturbance. It arises when relatively superficial nerve endings are stimulated in the skin or subcutaneous tissues, in the mucous membrane of the mouth or pharynx, in the synovia of superficial joints, in periosteum, and in serous membranes. It occurs also when the nerve trunk conveying fibres from superficial structures is directly invaded by disease. Muscular rigidity is an uncommon accompaniment except when joints or serous membranes are involved; then it occurs as a protective reflex.

The second type of pain is *deep*; whatever its intensity, from mild to excruciating, it is usually accompanied by nausea (and if severe by vomiting)—a " sickening pain ", by lowering of blood pressure, by sweating, and even by collapse; it is associated with rigidity of those muscles receiving their motor nerve supply from the segment of the cord bombarded by noxious influences from the diseased structure. Deep pain is, as we have earlier observed, difficult to localize accurately; it has a diffuse segmental distribution. It arises from muscles and tendons, deep periosteum and joints, and from viscera, and it may arise also when the nerve trunk carrying " pain " fibres from deep structures is affected by disease. Deep pain has the qualities here described, whether it arises from musculo-skeletal tissues or from viscera. By its character alone its source cannot be determined.

It would be wrong to regard these two qualities of pain as clear-cut types. They merge into one another; the nearer the surface the diseased structure, the more

closely the pain experienced corresponds to the superficial type; the deeper from the surface, the more is the quality of pain of the deep type.

We can then recognize *four main origins of pain*:

(*i*) *from the skin and superficial tissues*—e.g. buccal and pharyngeal mucous membrane, tibial periosteum, serous membranes, and superficial joints. This is pricking and burning in quality; the site of the noxious stimulus is well localized; there are no significant systemic reactions to the pain; muscular rigidity is rare, but may occur as a protective reflex.

(*ii*) *from nerves or spinal roots*. When these are mixed and receive fibres from both superficial and deep tissues, both superficial and deep pain may be felt in the area of distribution of the superficial nerve fibres, or segmentally if deep fibres be involved; when a spinal root is affected, the superficial and deep pain are felt segmentally; there is often an associated hypalgesia or analgesia and other signs of interruption of conduction in the nerve trunk, e.g. muscle wasting and abolition of reflexes.

(*iii*) *from deep structures*, including viscera, muscles, tendons, deep joints, periosteum, and bone. The pain is of deep, aching quality with segmental distribution, reflex muscle spasm, and systemic reactions.

(*iv*) *from cord or brain*, when the paths conveying pain impulses within the cord or brain are involved in disease, e.g. in new growths of the cord or thalamus. Here pain is often constant though subject to exacerbations without obvious cause, and when the thalamus is affected there may be marked emotional concomitants; the pain is often burning in type and may be associated with dysaesthesia and hypaesthesia; it extends over many segments, and sometimes almost half the body is involved on the contra-lateral side.

Clearly, unless a careful analysis is made of the pain so that the offending structure can be accurately indicted, much pain will pass as " rheumatic ". Hence the importance of discovering exactly from where the pain is arising.

Though the criteria just described will help us to determine whether the pain arises from superficial or deep disease, and in what segment or segments of the body the offending structures lie, they do not help us to specify the exact organ or tissue involved. To achieve this we must pass to another observation, namely, What are the factors which excite, aggravate or alleviate the pain ? For example, pain in the epigastrium may occur both from myocardial disease resulting in anoxia, or from peptic ulcer; the quality, localization and intensity of pain may be identical in both conditions, but the fact that the former is brought on by exertion and relieved by rest and trinitrin, whereas the latter is related to meals and eased by alkalies, firmly differentiates them. Similarly, pain in the groin may be due to a small hernia, to kidney or ovarian disease, to arthritis of the hip, or a host of other causes, but if we find that movement of the hip joint is limited and that it brings on the pain we are justified in looking to the hip as its origin. In the same way we can recognize pain arising from muscles, ligaments, and tendons, not only by local tenderness, but also by the effects of stretching or muscle contraction. I have elsewhere discussed how we may differentiate the various causes of backache by carrying out such tests (Cohen, 1948b). There is, however, one further observation of clinical importance which has often escaped notice, and yet is significant in the rheumatic field.

Some years ago, I pointed out that, just as anaesthetization of the superficial area in which pain from deep-seated disease is localized can abolish or diminish the pain, so irritation, by injection of hypertonic saline or blistering, of the superficial area in the segmental distribution of a diseased viscus can give rise to pain in that area though it had never earlier been a seat of pain (Cohen, 1947). Let me give an example. A patient suffering from angina of effort experiences pain in the lower sternal region and inner side of his left arm on walking 150 yards up a steady, slight incline; hypertonic saline injected into the right infra-clavicular region or blistering of the right elbow caused pain to appear in these areas after walking 80-100 yards up the same incline, and before his usual anginal pains had appeared. If, therefore, the patient has more than one lesion in the same or contiguous segments, e.g. angina and spondylitis, the pain of either may be more easily induced and thus treatment of the spondylitis can lessen the anginal tendency and *vice versa*.

I expressed doubts earlier about the value of objective tests designed to assess the intensity of pain; these tests have included various forms of algesiometer, and the injection of hypertonic saline solution, or the burning of a uniform area of skin with radiant heat, to determine the area and duration of discomfort. Yet it is clinically of signal importance to be able to decide about the intensity of pain and the patient's reaction to it. Certain rough tests can be applied. Does the pain interfere with work or sleep? Will aspirin control it or are stronger analgesics needed? The main factor to be appraised in assessing the significance of the intensity of pain is the patient's personality, for here we are faced with an ever-recurring problem in diagnosis, which is sometimes roughly posed by the phrase—" Is the pain ' real ' ? " Now this question has no meaning unless the word " real " be defined. To the victim all pain is " real " in the sense that he suffers; except, of course, to the malingerer who deliberately and consciously feigns illness in the hope of reward. But since pain is a percept, it may arise because the central receptor mechanism (" psyche ") is so sensitive that a stimulus, sufficiently slight to be ignored by a normal person, is experienced as " an unbearable pain ", or pain may even be a major complaint with no overt noxious stimulus. In so far as we identify the word " real " with an adequate organic cause (i.e. the presence of a diseased area capable of giving rise to adequate noxious stimuli) there are pains which are not " real ", in that many patients complain in bitter terms of severe pains for which we can find little or no adequate physical basis, and which we tend to attribute to the excessive receptivity of the sensorium; these are best named " psychogenic " pains.

We must not overlook, of course, the primary neuralgias which occur in the absence of physical signs of disease, but their character and distribution help us easily to differentiate them from " psychogenic " pains. The differentiating features of the primary neuralgias are these:

(*i*) The pains are paroxysmal, stabbing, and shock-like, in bouts lasting a few seconds separated by intervals of complete freedom from pain though of profound fear of its return, because of its excruciating severity;

(*ii*) stimulation of certain defined " trigger points " will excite a paroxysm of pain;

(*iii*) there is no evidence of disease of the nerve nor signs of interference with its motor, sensory, or secretory functions;
(*iv*) the onset is usually in middle or old age;
(*v*) attacks recur at intervals over many years without significant spread;
(*vi*) the distribution of pain corresponds exactly to the anatomical course of the affected nerve.

How then can we recognize pain which is predominantly psychogenic? The diagnosis must be based on positive features and not simply on the absence of organic disease, though this may well raise the suspicion in the first place. Among the criteria which I have found helpful are the following:

(*i*) The pain is almost invariably disabling, in the sense that it interferes with or prevents work, duty, or even pleasure.
(*ii*) It does not conform to any anatomical distribution. Indeed, its variable sites from day to day, or from hour to hour, are strikingly manifest, and it is associated with many contradictory phenomena, e.g. the painful area which is at one moment exquisitely sensitive to touch may be pressed upon without demur if the patient's attention is directed elsewhere.
(*iii*) It may be excited by fatigue or exhaustion, either mental or physical, but especially mental; pain due to organic disease may lead to exhaustion but does not follow it.
(*iv*) It commonly results from emotional stresses, conflicts, frustration, and neglect.
(*v*) It is commonly associated with other psychogenic disturbances, e.g. claustrophobia, and a constitutional inadequacy or predisposition to mental instability.
(*vi*) There is a history of manifold consultations, of innumerable investigations (the papers on which the results of these tests are recorded are often the presenting sign !), and of operations which have failed to benefit the patient. Such terms as " dropped stomach ", " adhesions ", " inflammation of the ovary ", etc., are names to which the patient has become so wedded that it is difficult to elicit the symptoms without the constant reiteration of a pet diagnostic label (but it should be remembered that there must be a first doctor whom the patient consults and that then this test will clearly not apply; he will be both lucky and wise if he avoids being the fount of iatrogenic illness !).
(*vii*) The patient almost always complains of the treatment meted out by former doctors, their negligence, and their ignorance (beware lest you be the next victim of his ire !).

None of these criteria is diagnostic but together they often paint an unmistakable picture.

Under what circumstances do these primarily psychogenic pains appear? Mainly in hysteria and the anxiety states but occasionally as a manifestation of a frank psychosis.

Using the word hysteria in its restricted sense of a psychogenic reaction designed to achieve a specific and personal aim, especially that of enabling the patient to escape from a difficulty, dilemma, or danger, or to fulfil a desire, of whose motivation he is in varying degrees unaware, we can recognize three types of pain in this category. Firstly, where there is a complaint of disease, and an hysterical version of the pain and other symptoms and signs which might be thought to be associated with it—so-called *simple conversion hysteria*; this is rare and easily recognized. Secondly, where old organic disease, e.g. injury, has been symptomless for years, but symptoms re-appear when the patient is faced with stress or hazard. Thirdly, where an injury, normally trivial, gives unduly prolonged disability and pain

in circumstances where stress and strain may be met with on recovery or where compensation for injury is hopefully, if subconsciously, anticipated.

The pains of anxiety states may well be due, in part, to muscle contraction and spasm—the somatic expression of the increased nervous tension which is occasioned by fear. Too often a depressive psychosis is overlooked as a cause of persistent psychogenic pain, though few would fail to appreciate the origin of the bizarre pains described with unrestrained verbal embellishments by the paranoidal valetudinarian and hypochondriac.

I have sought to show that the problems presented by the clinical analysis of pain can be solved only by those who look at the " whole " man. Those whose major field of medical practice is rheumatology must beware of the compartmental outlook, for their diagnostic field is general medicine. They must adopt the " synoptic " view and decide, if pain be the presenting symptom, whether it is dominantly physical or psychogenic. They must be prepared to spend time on taking the history and making a full examination, so that they can determine what accessory procedures, provided by *x* rays and clinical pathology, are necessary to reach a complete diagnosis, but they must not be bemused by the minor deviations from the normal which may be revealed by diagnostic machines, but which cannot possibly be related to the patient's complaints.

I do not claim to have presented any novel thesis; nor, indeed, were I able to do so, would this occasion have been appropriate. I have sought to review the more recent advances in our knowledge of pain and the help they give to its clinical interpretation, so that yet another step may be taken towards fulfilling Hilton's belief that " every pain has its distinct and pregnant signification if we will carefully search for it ".

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HEBERDEN ROUND

The Heberden Round was conducted by Professor L. S. P. Davidson in the Edinburgh Royal Infirmary on May 10, 1951. Eight cases were shown in the East Medical Theatre. The first four cases illustrated that pigmentation of the skin due to excess production of melanin can occur in four entirely unrelated diseases.

Case 1, Mrs. E.B., aged 32, pregnant.—She presented the typical clinical features of Addison's disease including pigmentation of the skin in the accepted situations. This was her second pregnancy, and the disease appeared to have followed immediately after the first pregnancy. She was treated with DOCA and salt. She was then put on to cortisone and at the time of the meeting was taking 15 mg. daily with DOCA twice

weekly, and her health was excellent. Professor Davidson mentioned how rare it was for patients with Addison's disease to become pregnant, only some 44 having been reported to date in the world's literature.

Case 2, Mrs. E.S., aged 37.—She had been admitted to hospital with features highly suggestive of Addison's disease, namely asthenia, loss of weight, anaemia, vomiting, low blood pressure, and marked pigmentation of the skin and mucous membranes. Chemical tests for Addison's disease including blood sugar tests, insulin sensitivity tests, and the Kepler test were negative. Because the liver and spleen were enlarged the diagnosis was changed to chronic hepatitis (cirrhosis of the liver), a condition in which pigmentation may occur. This diagnosis was not sustained since every type of liver function test was normal and porphyrins were absent from the urine. It was then discovered that the patient was an ephedrine addict and had been taking 30 to 40 $\frac{1}{2}$-gr. tablets daily for many years. It was suggested that the pigmentation was due to increased amounts of dihydroxyphenylalanine (DOPA) being available for the synthesis of melanin because reduced amounts were required by the body for the formation of adrenaline.

Case 3, Mrs. J. F., aged 47.—She had had jaundice caused by infective hepatitis in 1947. In 1949 she experienced pains in the back, and increased adiposity with sciatic pains and oedema of the legs. Hepatic function tests were all strongly positive and her liver and spleen were enlarged. There was radiological evidence of oesophageal varices; her globulin/albumin ratio was 2 : 1. Since 1947 she had noted a progressive darkening of the skin. Biopsy of the skin showed a pigment which proved to be melanin. Her blood sugar curve was normal. She was thought to be a case of chronic hepatic cirrhosis with skin pigmentation.

Case 4, Mrs. K.D., aged 32.—She was admitted to hospital in 1948 with progressive and severe weakness, diarrhoea, and abdominal pain, with paraesthesiae and muscle cramps. She had been working in a munition works. She was extremely anaemic (haemoglobin 20 per cent.); the marrow biopsy showed a megaloblastic marrow. The history was obtained that between the ages of 8 and 21 she had had frequent attacks of vomiting and diarrhoea associated with the passing of pale bulky stools. Accordingly the diagnosis was made of coeliac disease continuing into adult life. This patient also had patchy pigmentation with areas of leucoderma. She had never grown fully, was only 4 ft. 9 in. tall and weighed 4 st. 13 oz. She made a dramatic improvement on folic acid. Liver extracts and vitamin B12 had failed to improve her anaemia. Later her condition worsened with return of tetany and weakness. Her blood pressure dropped. This was found to be associated with a low serum-sodium; the administration of sodium citrate raised the blood pressure and improved the asthenia. The moral here was not to forget sodium deficiency in the malabsorption syndrome.

Case 5, Mrs. E.H., aged 60.—Hers was also a case of malabsorption syndrome associated with pigmentation. She was first admitted to hospital in 1940. She had lost 3 st. in weight and was passing eight sprue stools daily. She had spent 32 years in Ceylon and India but had never had diarrhoea there. She returned to the United Kingdom and remained well for 8 years before the onset of diarrhoea. Pigmentation was present on skin, nipples, and face. Cramps and tetany occurred from time to time. A microcytic anaemia passed through a dimorphic phase over the years to megaloblastic anaemia. Six times she had been admitted to hospital severely ill in relapse and suffering from diarrhoea and multiple deficiencies, and the prognosis appeared to be very bad indeed. At this time she was vaccinated against smallpox. At the sites of vaccination she developed a marked staphylococcal cellulitis with high fever, to be followed by suppurative parotitis which had to be surgically drained. From that time onwards she rapidly improved in health without any further treatment, so that she gained 4 st. in 4 months, and was able to eat anything she liked without precipitating diarrhoea. She has now been in perfect health for the last

7 years. It was suggested that this extraordinary cure might be due to a successful adaptation to a severe skin reaction which had stimulated the patient's output of cortisone. On this basis therefore trials of cortisone and ACTH were suggested for the sprue syndrome.

Case 6, J.A., a sailor, aged 43, who had since died.—He had developed the malabsorption syndrome due to intestinal obstruction secondary to tuberculosis. This patient then proceeded to develop signs of subacute combined degeneration of the spinal cord which were confirmed microscopically. The stomach was histologically normal.

Case 7, J.H., aged 55.—He complained of haemorrhages into the skin from the gums and elsewhere of 5 weeks' duration. He was found to have a palpable spleen; the white cells were normal but the platelets were reduced to 25,000 per c.mm. Marrow biopsy showed plenty of megakaryocytes. No aetiological agent was discovered. A diagnosis of idiopathic thrombocytopenic purpura was made. The severe bleeding was not controlled by local measures or blood transfusions given on three occasions. Accordingly, ACTH was given, and bleeding ceased within 12 hours, never to return. No change, however, was noticed in the bleeding time, capillary resistance, or platelet count to explain the cessation of bleeding. After 60 days all these features had returned to normal. Professor Davidson asked if this remarkable response was a spontaneous remission or therapeutically induced.

Case 8, Mrs. J.G., aged 21.—She had been given liver extract elsewhere for 11 years although she proved to be suffering from haemolytic anaemia (acholuric jaundice). She had become pregnant and during her pregnancy developed a severe megaloblastic anaemia. The marrow was returned to the normoblastic pattern by folic acid, 10 mg. three times daily, and she had a normal delivery of a normal child. Professor Davidson said that this was the only case of haemolytic anaemia which he had seen in 30 years which had developed a classical megaloblastic anaemia.

The President, Sir Henry Cohen, thanked Professor Davidson for his excellent demonstrations.

During the afternoon members visited the wards and ancillary departments at the Rheumatic Unit in the Northern General Hospital; demonstrations and cases of clinical interest were shown, and the following short communications were read:

Steroid Metabolism in the Chronic Rheumatic Diseases, by Professor G. F. Marrian.

A brief account was given of the work carried out in collaboration with Dr. Duthie and Dr. Sinclair in the metabolism of administered progesterone in rheumatoid arthritis. In severe cases clear evidence has been obtained of an abnormality in the metabolism of this hormone, but the exact significance of this finding is as yet rather obscure.

An outline was also given of recent work carried out on the quantitative determination in urine of metabolites of the adrenocortical hormones. It was stressed that by existing methods only a small fraction of these urinary metabolites are actually determined.

Clinical Trials of ACTH and Cortisone, by Dr. W. R. M. Alexander.

The methods used in the clinical assessment of two cases of rheumatoid arthritis and one case of gout were described, and differences in certain effects of the two hormones in the same patient were discussed.

C-Reactive Protein in Rheumatic Diseases, by Dr. Alan G. S. Hill.

Results were presented of tests for C-reactive protein in serum from examples of various types of rheumatic disease. Positive results were obtained in all active cases of rheumatic fever, in most active cases of rheumatoid arthritis, and in gout during acute episodes. C-reactive protein was absent in osteo-arthritis, in a small group of cases of acute disseminated lupus erythematosus (except during incidents of superadded bacterial

infection), in dermatomyositis, and in scleroderma. In cases of rheumatoid arthritis treated with ACTH or cortisone, C-reactive protein rapidly disappeared. It was suggested that the test might be profitably used in assessing the response to other therapeutic agents with possible anti-rheumatic activity.

Radiotherapy in Ankylosing Spondylitis, by Dr. J. L. Potter.

An investigation of the clinical, haematological, and biochemical effects of radiotherapy in ten cases of ankylosing spondylitis and one case of spinal osteo-arthritis were described, and the results reported. It was suggested that the early clinical improvement observed may be mediated partly by an increased adreno-cortical activity, and further experiments to confirm this hypothesis were discussed.

The Sterno-Manubrial Joint in Rheumatoid Arthritis and Ankylosing Spondylitis, by Dr. Bruce Cruickshank.

The histological changes which occur in the manubrio-sternal joint and in symphysis pubis in ankylosing spondylitis were discussed, illustrated, and correlated with the radiological appearances. It was suggested that the pathological process in these cartilaginous joints is analogous to that seen in synovial joints in the disease.

Clinical and Metabolic Effects of Glutathione in Rheumatoid Arthritis, by Dr. A. P. Meiklejohn.

The clinical effect obtained by the intravenous administration of glutathione to a case of rheumatoid arthritis was described, but it was reported that attempts to repeat this effect had met with failure. The theoretical implications were discussed with special reference to the utilization of vitamin C in rheumatoid arthritis.

A Method of Demonstrating the Union of Antibody and Antigen in Tissues, by Dr. Alan G. S. Hill.

The use of fluorescein-tagged antibody as a specific cytochemical reagent for the detection of antigenic material in tissues was described. Illustrations were shown of results obtained in a study of the localization of an injected bacterial polysaccharide in animal tissues. The possibility of applying the method to a study of the rheumatic diseases was discussed.

CLINICAL MEETING

The Heberden Society met at the Ciba Foundation, 41 Portland Place, London, W.1, on July 27, 1951. The President, Professor Sir Henry Cohen, was in the Chair.

Dr. W. H. Bradley gave a paper on **The Antagonism between Jaundice and Rheumatism.** He said that intermittent and spontaneous recovery was an unpredictable feature of the chronic rheumatic diseases, but that there was a persistent claim that certain acute infections, pregnancy, and jaundice antagonized rheumatism. The first important contribution to this subject had been made in 1933 by Hench, who by 1940 had collected 72 cases in which jaundice appeared to ameliorate rheumatism and wrote that:

Within the bodies of patients who have even the severest arthritis powerful forces lie dormant which merely await proper stimulation.

Light on the subject had since come from:

(*a*) experimental induction of hyperbilirubinuria.

(*b*) jaundice incidental to therapy with synthetic analgesic drugs: Lactophen, Atophan, Nirvanol, and, in a special class, gold.

The transmission of hepatitis due to biological agents had first been attempted in 1943 as part of the work of the Medical Research Council Jaundice Committee, and transmission of epidemic hepatitis and homologous serum jaundice to rheumatoids had been effected. The results supported Hench's opinion that:

> Somehow hepatitis provides a stimulant, following which a rapid and dramatic even if temporary recovery from arthritis may occur.

The following points regarding the ameliorative effect were noted by the Committee:

(*i*) it occurred early in the pre-icteric phase of hepatitis when erythematous rashes might also occur in hepatitis, or in Lactophen jaundice, or with Atophan;
(*ii*) it appeared to be independent of the presence of jaundice or of the serum bilirubin level, anorexia or starvation, fever, decubitus, and absence of bile from the gut;
(*iii*) it was not merely the result of a depression of the pain threshold;
(*iv*) it occurred only in the presence of rheumatic activity, and quiescent and burnt-out rheumatoids did not benefit;
(*v*) an impression was obtained that return of rheumatic activity depended upon restoration of normal hepatic functions.

The effect of hepatitis closely resembled the effect of cortisone, and since there was a possibility that both these "cures" were brought about in the same way, a search for common factors should be instructive. A comparison of total circulating protein in hepatitis and in rheumatoid arthritis appeared to give a lead, and it seemed that the collagenolytic effect of cortisone and its influence on antibody productions was worth exploration.

For the time being, both cortisone and hepatitis should be regarded as no more than research tools—both dangerous—and special precautions were necessary if the hepatitis virus was used in clinical investigation.

Drs E. G. L. Bywaters and A. St. J. Dixon presented a paper on **Intra-Articular Cortisone in Rheumatoid Arthritis.** The patients selected for this study had symmetrical effusions in the knees due to rheumatoid arthritis. One knee received injections of intra-articular cortisone acetate, and the other knee received blank injections. The injections were made after complete aspiration of the joint fluid. Comparison between the fluids found in both knees 24 and 48 hrs later showed that cortisone acetate reduced the volume of the fluid formed in the treated knee and increased its viscosity. The increase of viscosity was shown to be due to an increased polymerization of hyaluronic acid.

Serial injections into the knee joint at 4-day intervals, using increasing doses of cortisone acetate (with the contra-lateral knee as a control), showed that it was possible, with adequate dose, almost completely to inhibit the re-formation of joint fluid; and that the little which was re-formed was of high viscosity. A further series of injections was given (again treating one knee and using the other as a control). After a control period the patient was given a short course of systemic salicylates. No additive effect on salicylates and cortisone could be demonstrated.

On one patient the least intra-articular dose which could be shown to produce an alteration in joint fluid was 20 mg., and the greatest dose which could be injected into the knee joint without systemic effects was 160 mg.

Other results of the intra-articular administration of cortisone were:

(*i*) decrease in the total white-cell count with relative increase in lymphocytes in the fluid;
(*ii*) no change in the total and differential protein content in the fluid;
(*iii*) no change in the fluid glucosamine or glucose;
(*iv*) alteration in the type of clot formed with acetic acid when added to the joint fluid (indicating an increase of polymerization of hyaluronic acid).

However, *in vitro*, the addition of cortisone acetate suspension to joint fluid showed that the former is precipitated rapidly as fibrin-covered aggregates. This might explain how it was that the quantitative effect of any particular dose of intra-articular cortisone could not be forecast with certainty.

DR. FRED WRIGLEY gave a paper on **Experimental Arthritis: Its Production and Measurement.** Work on the production of joint swelling in animals had first been started by making use of the pleuropneumonia-like organism. Early experiences showed that abscesses were frequently produced in the animals at the same time as the joint swelling. Animal passage, sub-culture, and freeze-drying, had been employed, and a preparation finally obtained which, on injection, caused joint swelling without abscess formation. A study of this condition had shown that it was capable of spontaneous resolution, and therefore the animals were not used for the screening of drugs.

" Formalin arthritis " had been produced in a large number of animals, and although peri-articular swelling was apparent, there was no dramatic alteration in the condition, nor any prevention of the development of the condition when ACTH, cortisone, DOCA, and DOCA and ascorbic acid were administered. These results were controlled by:

(*a*) uninjected animals;
(*b*) formalin-injected animals without further medication.

Throughout the work it was obvious that a method of measuring joint swelling must be devised, and a method was ultimately adopted in which the animal's limb was exposed to light over photographic paper and a silhouette obtained. The shapes from different positions were weighed and a figure obtained representing the volume of the limb. These very readily allowed a group comparison, and showed up changes in limb volume. The method was checked by comparison with an inanimate object and shown to be accurate to within plus or minus 6 per cent.

DR. C. J. M. CLARK gave a paper entitled **Observations on Rose's Agglutination Test in Rheumatoid Arthritis.** The development of Rose's sheep-cell agglutination test was described, and the results in a series of cases discussed. In the technique used the heterophil agglutinin was not absorbed and a 2-hr reading was used. A titre of 1 in 32 or over was considered positive. There were no positive reactions among 42 patients with ankylosing spondylitis. Two out of twenty patients with miscellaneous arthritic lesions had positive titres. Both these appeared clinically to be cases of palindromic rheumatism but their follow-up was short.

Out of 100 patients with rheumatoid arthritis, 33 had positive reactions and an analysis was made of these cases. Graphs showed that there was no direct relation between the titre and any of the following factors:

haemoglobin	serum colloidal gold
packed-cell volume	thymol flocculation
erythrocyte sedimentation rate	thymol turbidity
serum albumin	zinc sulphate turbidity
serum globulin	ammonium sulphate turbidity.

In addition, no correlation with changes in plasma fibrinogen, splenic, or lymph-node enlargement, nodule formation, or gold therapy could be established, but it did appear that only low titres were found in cases with a long history of arthritis who had a positive agglutination test.

No obvious relationship to the activity of disease could be established, but preliminary results did suggest that ACTH and cortisone reduced the titre of the positive reactions in some cases.

DR. D. LONG gave a paper on **Cortisone and Allergy** which is to be published in full in a later issue of the *Annals*.

ANTI-RHEUMATIC ACTIVITY OF SEVERAL STEROIDS

BY

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One of the problems in rheumatology research is the variation in reported results of the anti-rheumatic effects of new substances. This paper presents methods of eliminating the variables which are felt to be responsible for the diversity of views of investigators in this field, together with data on the relative anti-rheumatic activity of several steroids. The effect of ACTH and cortisone, pregnenolone, acetoxypregnenolone, testosterone, and other steroids has already been studied in rheumatoid arthritis, but a quantitative assay of their anti-rheumatic activity is needed. The more definite anti-rheumatic effect of cortisone and ACTH offers a good standard of comparison. Previous studies have indicated interesting metabolic effects of testosterone in rheumatoid arthritis, and a further study of the possible anti-rheumatic activity of testosterone was therefore undertaken.

It is apparent that the basis of the variation in the reported anti-rheumatic effects of new substances lies in certain uncontrolled variables, of which the following are the most significant in rheumatoid arthritis:

(1) psychic factors,
(2) spontaneous variation in disease activity,
(3) degree of activity of the disease,
(4) pre-existing endocrine imbalance.

(1) The importance of psychic factors has been much emphasized. Any experiment must involve methods of controlling this factor. Most important of these is the selection of patients whose disease has been followed for a long period and whose response to other forms of therapy (especially to placebo administration) under conditions identical with those of the experiment is known.

(2) In a disease with so great an incidence of spontaneous remission or improvement as rheumatoid arthritis (Short and Bauer, 1948), it is well to select patients who have had little variation for a long time, and to prefer a few, long-term studies to numerous, short-term observations.

(3) With present methods the severity of the disease can be estimated only from the signs and symptoms, elevation of sedimentation rate, rate of progression, and duration of disease.

(4) Should endocrine imbalance be involved in the pathogenesis of rheumatoid arthritis (Hench and others, 1949; Liefmann, 1950), the quantitative degree of imbalance of the one or more hormones involved varies in different patients.

* Supported by a grant from the Canadian Arthritis and Rheumatism Association.

Thus the results of studies in rheumatoid arthritis differ widely according to the selection of patients. The anti-rheumatic effect of a substance to be tested may appear to be very marked in a mildly active, easily reversible case and may be undetectable in a severely active case.

Assay of New and Untested Steroids in Terms of the Anti-Rheumatic Activity of Cortisone by the Method of Partial Substitution

Theoretical Bases of Study.—In order to standardize the anti-rheumatic steroids, it is highly desirable that the mechanism of action of any anti-rheumatic compound be known. For example, Hench and others (1949) established that the most active anti-rheumatic steroids are the glucocorticoids (17-11-oxycorticosteroids).

However, the anti-rheumatic effects of compound E (cortisone) and compound F have not been shown to be mediated through their action on carbohydrate metabolism or even to be proportional to this activity. If this were so, a simple means of assaying and developing new anti-rheumatic steroids might be readily available. To avoid the necessity of making any unfounded assumption regarding the mechanism of action of the steroids to be tested for anti-rheumatic activity, an empirical method of comparing unknown steroids with cortisone as a standard has been developed. Let us suppose that with a standard dose of cortisone (e.g. 100 mg./24 hrs) a remission is obtained in a case of rheumatoid arthritis. An aliquot is then subtracted from the dose and an unknown steroid substituted for it.

For example, the dose of cortisone may be lowered to 25 mg./24 hr until exacerbation with minimal arthritis signs and symptoms recurs; the unknown steroid is then added in increasing amounts until remission again occurs (or negative results are obtained). The amount of " unknown " necessary to effect remission is then equated to the aliquot of cortisone replaced (in our example 75 mg.), and the anti-rheumatic activity of the unknown is related to that of cortisone, taking the latter as 100 per cent. For example, if 200 mg. of the unknown be required to cause remission, then $\frac{75}{200} \times 100 = x$ per cent.

An assumption is inherent in this method, namely that the unknown and cortisone both have the same mechanism of action. Let us suppose, as a purely hypothetical case, that this consists in the decreased activity of an enzyme, both the unknown and cortisone acting on the same enzyme to alter its activity. If however, different mechanisms were involved in the anti-rheumatic effects of the steroids, then their effects might even be antagonistic and this method of comparison would not be valid.

Practical Application.—The anti-rheumatic activity of testosterone, pregnenolone, and acetoxypregnenolone* have been tested by the above method.

A series of patients, carefully selected as outlined above, is brought into a state of " minimal disease activity " by means of a dose of cortisone just below that required to control the disease; the unknown steroid is then added, and its minimal effectivity assessed. Thus the third and perhaps the fourth of the variables listed above is controlled. If the drug under test is unable to reverse the minimal disease activity it can be assumed that it has no cortisone-like anti-rheumatic action.

* The cortisone, pregnenolone, and acetoxypregnenolone were all aqueous crystalline suspensions.

Procedure

Out of fifty cases seen in the Arthritis Clinic of the Out-Patient Department of the Royal Victoria Hospital, Montreal, five rheumatoid arthritis patients were selected who fulfilled the criteria discussed above:

(1) they had unremitting rheumatoid arthritis activity,
(2) the erythrocyte sedimentation rate remained abnormally high,
(3) they had been seen weekly in the Out-Patient Department for a period of 2 to 10 years before the present study was undertaken,
(4) their previous response to other forms of therapy was known,
(5) they all had the most severe type of rheumatoid arthritis.

During these investigations the patients were seen daily by the writer, and the erythrocyte sedimentation rate was determined, at first daily and then three times per week. Blood electrolyte and proteins were determined, and urinary 17-keto-steroid, glucocorticoid, and other determinations made from time to time, as the clinical course indicated.

A complete physical examination was made daily and the subjective pain experienced by the patient during the previous 24 hours was denoted as:

\+ minimal,
\++ moderate,
\+++ severe but bearable,
\++++ unbearably severe.

This method took into account the degree of articular swelling, range of joint-motion (tested in the Physiotherapy Department), and muscle function (e.g., tests with the hand dynamometer in the Neurological Department). The cases were also assessed according to the classification accepted by the New York Rheumatism Association and American Rheumatism Association (Steinbrocker and others, 1949).

The data given below cover a period of 10 months' clinical study. The patients' reactions to various types and intervals of dosage are presented in great detail so that the niceties of the grades of remission and exacerbation which resulted may be observed. The treatment, sedimentation rate, and severity of symptoms in Cases 1, 2, and 3 are set out graphically in the three Figures.

Case Reports

Case 1 (F.2371, see Fig. 1).—28-year-old male, with 10-years' history of rheumatoid arthritis of a slowly progressive type which had remained continuously active with one or more joints acutely involved during the entire time.

Disease Activity.—The tarsal and metatarsal joints were involved first, the disease gradually progressing until the patient was unable to walk unassisted. There were typical *x*-ray changes in the involved joints, with osteoporosis and narrowing and clouding of the joint spaces. There had been varying disease activity in both knees with soft-tissue swelling, and at the time of the experiment there was an accumulation of fluid in both knee joints, and in the right quadriceps muscle giving the knee the size and shape of a football. Both wrists were ankylosed with involvement of all the carpal and metacarpal bones; there were typical *x*-ray changes and gross deformities of the hands with ulnar deviation and muscle atrophy. There was acute pain in both

wrists but little swelling. The third proximal interphalangeal joint of the right hand showed acute swelling, redness, and pain. Both elbow joints showed swelling, pain, tenderness, and limitation of extension to 45°. There was extreme muscle atrophy throughout the body, which was especially marked in the upper and lower limbs.

Appearance.—This patient has eunuchoid proportions with short trunk, and long upper and lower extremities. The hands and feet are gracile and elongated, size 14 shoe. He has never had to shave, there is scant axillary and pubic hair, and no hair on the trunk and extremities.

History.—The patient had been observed weekly in the out-patient department arthritis clinic for 5 years, during which the sedimentation rate varied from 14 to 28 mm. with only occasional normal values. At all times during this five-year period the patient had unremitting signs and symptoms of active rheumatoid arthritis.

Laboratory Findings.—Serum electrolytes normal with sodium at lower limit of normal 317 mg. per cent. (normal 320-340).

Urinary 17-ketosteroid excretion 7·6 mg./24 hrs (normal 5-10); glucocorticoids 30 glycogenic units/24 hrs (normal 40-80); gonadotropins positive at 52·8μ, stimulated at 105·6μ (normal, positive at 26).

Oestrogen positive at 80μ, stimulated at 160μ (normal 40-60).

Increased tolerance to glucose, fasting 74 mg. per cent., ½ hr 105, 1 hr 85, 1½ hrs 95, 2 hrs 89, 2½ hrs 99 (flat-type curve seen in Addison's disease, etc.).

Serum total cholesterol low, 123 mg. per cent. (normal 150-250).

Haemoglobin 73 per cent.

Red blood count 3,750,000.

Assessment.—At the start of the present study (January 26, 1950) the disease activity was +++, with continuous severe pain in the involved joints, the patient being able to sleep only a few hours at night. He was unable to walk unassisted and unable to stand in the morning, having to be assisted from the bed to the bath. Elbows, feet, and ankles were all acutely active. A large amount of fluid was detectable in the left knee and surrounding soft tissues. Sedimentation rate 16 (corrected Wintrobe). This patient was classified as " Stage 4, active, Class 4 ".

Therapy.—This patient first received testosterone propionate solution in oil intramuscularly twice weekly, Injection 1—200 mg., 2—250 mg., 3—500 mg., 4—200 mg., 5—250 mg. There was no cessation of pain, no change in swelling, heat, redness, or tenderness in the involved joints. The sedimentation rate during the second week fell from an initial value of 16 mm. (uncorrected 23), to 11 mm. (uncorrected 17). During the second week, the left ankle joint became more severely painful; there was increase in swelling and pain in the right knee joint, and severe pain in the elbow and hands in the mornings. The patient was objectively and subjectively worse; therefore therapy was discontinued (Grade 4 response).

After one week without treatment the sedimentation rate rose to 20 mm. (uncorrected 27). Ascorbic acid was then given, 1 g./24 hrs, intravenously, after which a decrease of fluid in the right knee was observed; this was now barely detectable but remained as before in the right quadriceps. Upon repeated injections of ascorbic acid 1 g. there was no change in pain or other symptoms, or in the inflammation in the involved joints.

The patient was then given 10 mg. DOCA in oil intramuscularly, followed by 1 g. ascorbic acid intravenously. After the second daily injection there was no palpable fluid in the right knee joint. There was also great subjective improvement, the patient commenting that he was able to dress himself in the morning for the first time for many years and was able to walk unassisted on rising in the morning. However, the sedimentation rate remained elevated, 16 mm. (uncorrected 24). There was no pain in the ankles or feet. No further therapy was given after the second injection and the patient's pains and other signs and symptoms of rheumatoid arthritis returned as before.

This time 250 mg. testosterone was given intramuscularly and 1 g. ascorbic acid.

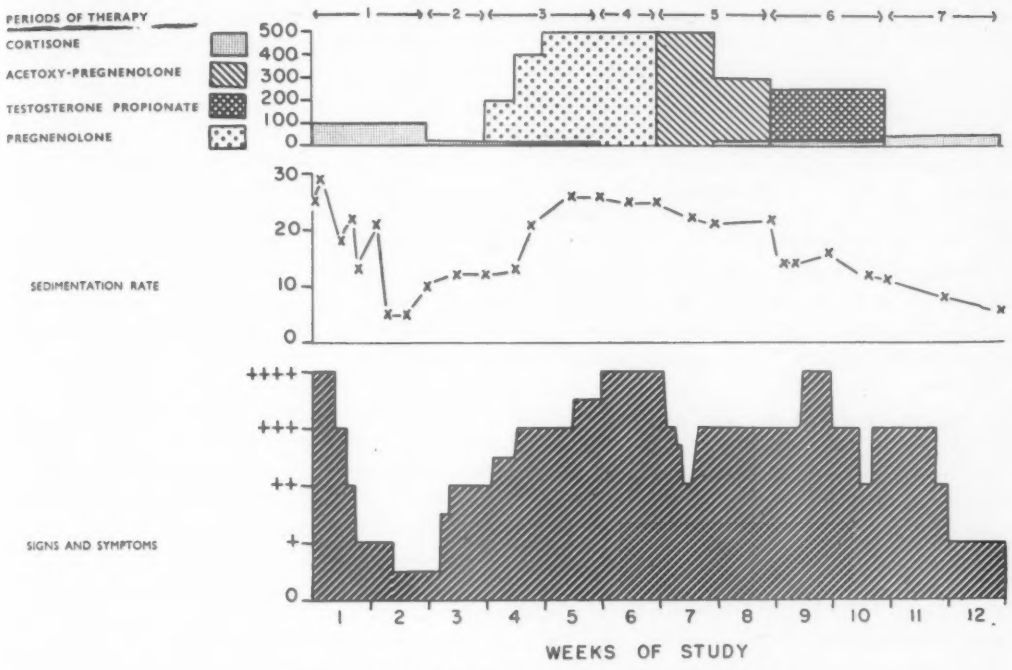

FIG. 1.—Case 1 (F.2371), rheumatoid arthritis.

Periods of therapy:

(1) Disease controlled on cortisone acetate 100 mg./24 hrs.
(2) Cortisone 25 mg./24 hrs. Minimal disease activity.
(3) Simultaneous administration of pregnenolone 200, 400, 500 mg./24 hrs. No beneficial effect.
(4) Cortisone discontinued. Pregnenolone 500 mg./24 hrs. Severe exacerbation.
(5) Acetoxypregnenolone 500 mg./24 hrs. Little beneficial effect until re-institution of 25 mg. cortisone.
(6) Simultaneous administration of 25 mg. cortisone and testosterone propionate 250 mg./24 hrs. No beneficial effect.
(7) Cortisone 50 mg./24 hrs. Remission.

24 hrs later there was only minimal pain in the involved joints and the patient was again able to walk unassisted. After the third injection testosterone was discontinued and ascorbic acid 1 g./24 hrs was given intravenously for one week, at the end of which he felt subjectively improved with absence of pain in the elbows and hands, and greater range of movement in the fingers, but residual pain remained in the involved joints on active motion and a small amount of fluid remained in the right quadriceps muscle. However, several involved joints were acutely active, with severe pain, including the second and third proximal interphalangeal joints of the right hand and both elbows (Grade 3 response).

After a two-week control period, there was ++++ activity in all the involved joints, with severe, constant, unbearable pain, requiring frequent analgesics. He was unable to walk because of severe pain and swelling in the knee and ankle joints, and severe pain in both heels. The right calf muscles were markedly oedematous, and it was possible to depress the quadriceps muscle 2 inches with the ruler.

Fig. 1 (1). He was next put on cortisone acetate in aqueous suspension—100 mg./24 hrs intramuscularly. The sedimentation rate at the beginning of cortisone therapy was 26 mm. (uncorrected 38), and on the second day of therapy 30 mm. (uncorrected 47). After the third injection of cortisone there was some objective and subjective improvement, and patient was able to stop taking analgesics and to sleep better. There was almost

complete disappearance of swelling in the right knee but no change in the quadriceps. After 5 days of cortisone therapy, heat and tenderness disappeared from the right knee. There was now 10° flexion in the left wrist, whereas it was motionless before. Swelling in the ankles had completely disappeared, the patient being able to walk half a mile with only moderate pain, and there was a 20° range of flexion of the ankles, but 1 inch of palpable fluid remained in the quadriceps. After one week there was only + disease activity in the involved joints with minimal residual pain, swelling, and tenderness, and on the 10th day there was further improvement, the patient being able to run for the first time since the onset of his disease and to walk vigorously for a mile and a half. On the eighth day the sedimentation rate was still elevated (21 mm., uncorrected 34), but on the ninth day it fell to normal values (6 mm., uncorrected 16).

At the end of the second week there were only minimal residual signs and symptoms of rheumatoid arthritis and the sedimentation rate was normal (Grade 1 response, i.e., complete remission).

Fig. 1 (2). During the third week the dose was reduced to 25 mg./24 hrs, and on the third day a little palpable fluid returned in the right knee, with moderate pain in the involved joints on active motion. Thus the disease activity was + (i.e., equal to *minimal disease activity*) on cortisone 25 mg./24 hrs. The sedimentation rate had risen to 12 mm. (uncorrected 22), but the patient was sleeping well, without analgesics.

Fig. 1 (3). To find whether pregnenolone, acetoxypregnenolone, or testosterone could reduce this minimal disease activity, cortisone 25 mg./24 hrs was continued during the fourth and fifth weeks, but combined with pregnenolone crystalline in aqueous suspension intramuscularly 200-500 mg./24 hrs. Despite the large dose of pregnenolone given in combination with cortisone, an acute exacerbation occurred, with severe pain in elbows, knees, ankles, and feet, and the patient became bed-ridden. His knees and ankles were swollen and inflamed, and the swelling and tenderness in the elbows were more severe than before treatment.

Fig. 1 (4). During the sixth week he was given pregnenolone 500 mg./24 hrs; the arthritis activity was ++++ and the patient was unable to sleep because of severe pain; the objective and subjective changes in the involved joints indicated a severe exacerbation (Grade 4 response).

Fig. 1 (5). In the seventh week he received acetoxypregnenolone intramuscularly 300-500 mg./24 hrs. The sedimentation rate had risen during the sixth week to 25 mm. (uncorrected 36). During the eighth week this was combined with cortisone 25 mg./24 hrs, and there was some decrease in the severity of the objective and the subjective findings, but inflammatory signs in the involved joints were unchanged. There was much palpable fluid in the right knee and quadriceps muscle, with constant severe pain in the knees, ankles, and elbows. The sedimentation rate remained elevated (22 mm., uncorrected 35). Subcutaneous nodules in the region of both elbows were noted for the first time. The patient complained that the pain in his elbows was worse during acetoxypregnenolone therapy (Grade 4 response).

Fig. 1 (6). During the ninth and tenth weeks testosterone propionate 250 mg./24 hrs was given intramuscularly with the cortisone 25 mg./24 hrs. After the fourth injection of testosterone there was a severe exacerbation with ++++ arthritis activity. The elbows, ankles, and feet were severely painful and swollen, and the patient was unable to walk, to care for himself, or to sleep. The sedimentation rate at this time, however, had returned to normal (6 mm., uncorrected 16). During the second week of combined testosterone and cortisone therapy, swelling in the involved joints subsided but the pain continued to be severe and constant. The subcutaneous nodules were larger, and he complained that he had more pain in his wrists and fingers than previously. There was much palpable fluid in the right knee and right quadriceps, seborrhoeic acne of the nose and surrounding tissue. At the end of the tenth week the sedimentation rate remained

normal (11 mm., uncorrected 25), but the signs and symptoms of rheumatoid activity were more severe than when on 25 mg. cortisone alone (Grade 4 response).

Fig. 1 (7). Testosterone was then discontinued and the cortisone increased to 50 mg./24 hrs. There was no change until the end of the second week when the pain diminished progressively until the 17th day, when there were only residual pains in the involved joints, especially in the ankles, on active motion. Because of these slight pains the patient was unable to walk as well as when he was on cortisone 100 mg./24 hrs, but at rest he was symptomless; he could care for himself, walk to the hospital, and engage in limited social activities.

To decrease the visits to the out-patient department, 100 mg. cortisone was given every other day, but at the end of the third week of this regime, moderate pain and swelling returned in the knees and ankles, and walking became more difficult. After 6 weeks of injections every other day the fluid in the right quadriceps and knee joint was as abundant as ever and frequent analgesics were required.

During the seventh and eighth weeks 100 mg. cortisone was given every day, but the exacerbation continued and severe pain extended to the elbow and wrists, but at the end of the eighth week he once again became symptom-free, which indicates that daily administration of cortisone is required in this case to maintain remission. He has since been maintained symptom-free with only occasional pain for 2 months on a daily dose of 50 mg. cortisone intramuscularly, but it seems necessary in this case to continue daily cortisone injections indefinitely.

Case 2 (C.5296, see Fig. 2).—55-year-old male, with rheumatoid arthritis of 12 years' duration. He had been observed in the arthritis clinic weekly for 6 years except when admitted to the Royal Victoria Hospital in 1946 and 1949.

Disease Activity.—The rheumatoid arthritis had progressed slowly and continuously involving joints of the feet, ankles, knees, hands, wrists, and shoulders. The musculature was generally well preserved with little local atrophy. Arthritis of the wrists, ankles, knees, hands, and shoulders had remained active during the entire time of observation, with moderate to severe pain, swelling, and limitation of motion. The wrists were immobile without bony ankylosis, and the knees swollen and acutely painful and tender.

History.—There had been no response to previous treatment, including gold and physiotherapy. The sedimentation rate had remained elevated (24 to 40 mm., corrected Wintrobe). The patient had recently been hospitalized at the Royal Victoria Hospital and treated with ACTH for one week (100 mg./24 hrs) with disappearance of all pain and swelling and return of use of the involved joints.* Upon withdrawal of ACTH, his condition became exacerbated.

Special Diet.—At the start of this present study the patient was placed on a special high protein, low calorie diet, to elicit an increased adrenocortical secretion. Before treatment the 17-ketosteroid urinary excretion and glucocorticoid excretion had been low. The diet consisted of 1,800 to 2,000 calories per day, 300-400 g. protein per day. Synthetically flavoured gelatine made up a large fraction of the protein in addition to food with a high protein content (which alone is too high in calories). Supplementary vitamins and essential amino-acids were added.

Laboratory Findings.—Daily urinary excretion of 17-ketosteroids had ranged from 4 to 10·8 mg./24 hrs, with one isolated finding at 15·2 mg./24 hrs; but during the first week of high-protein diet there was no significant rise and 17-ketosteroid excretion varied from 4·6 to 10·6 mg./24 hrs; during the second week there was a peak at 13·3 mg./24 hrs, and during the third week a peak at 16·4 mg./24 hrs. The glucocorticoid excretion level in this patient had been low (16 and 19 glycogenic units/24 hrs, normal 40 to 80), but during the high-protein diet period this rose to 32 and 40 glycogen units/24 hrs. A paradoxical finding in glucocorticoid excretion occurred subsequently while the patient was on testosterone 100 mg./24 hrs; on the third and fourth day,

* This ACTH study is reported elsewhere.

during which times there was no clinical improvement in the rheumatoid arthritis, the glucocorticoid excretion rose to 72 glycogen units/24 hrs. During an exacerbation of the disease in this patient the glucocorticoid level was higher than it was during a remission induced by ACTH (exacerbation level, 69 and 65 glycogen units/24 hrs; remission level, 26, 48, and 30 glycogen units/24 hrs).*

Assessment.—After cessation of the special diet there was a 4-week control period during which the inflammation in the involved joints remained severe and the sedimentation rate rose to 38 mm. (uncorrected 40). The patient complained of severe pains in the wrists, elbows, and knees (disease activity +++). He was able to perform only the minimal activities of self care and to hobble with the aid of a cane. This patient was classified as " Stage 3, active, Class 3 ".

Therapy.—He was placed on 250 mg. testosterone propionate intramuscularly twice a week. There was an immediate improvement in ability to walk for several hours after each injection, when the patient was able to " throw away his cane ". This was very likely a " psychogenic improvement ", since after the fourth injection the degree of inflammation of the joints was ++++, he was unable to move his ankles, and there was an increase in joint fluid and signs of inflammation. Extreme pain and swelling continued in the wrists and shoulders, the patient was unable to walk, and the sedimentation rate remained high (26 mm.); thus testosterone therapy was discontinued. At this time he was unable to bear weight on standing without ++++ pain.

To investigate the temporary post-injection improvement which followed testosterone, the patient was told he was to receive a combination therapy and was given one injection of distilled water intravenously and one intramuscularly. Ten minutes after injection he was able to walk without his cane, with only a moderate amount of pain, and greatly increased range in motion and freedom of movement in both knees.

He then received DOCA 5 mg. intravenously simultaneously with 1 g. ascorbic acid intramuscularly, after which there was no change in signs or symptoms beyond that which had occurred with distilled water. The same evening, 6 hours after the placebo, signs and symptoms returned to ++++.

During a one-week control period the signs and symptoms remained ++++, with severe pain and inflammation in the involved joints, and sedimentation rate moderately elevated (14 mm., uncorrected 16).

He then received a combined daily injection of 5 mg. DOCA and 1 g. ascorbic acid intramuscularly, one week after which there was no subjective or objective change in signs or symptoms ++++, and the sedimentation rate remained elevated (22 mm., uncorrected 20). However, on several occasions there was temporary subjective relief of symptoms for 6 hours after injection equal to that which occurred after the placebo and testosterone injections. The amount of palpable fluid in the knees and wrist was unchanged (Grade 4 response).

Fig. 2 (1). He was then placed on cortisone acetate in aqueous suspension intramuscularly 100 mg./24 hrs. On the fifth day the pain in the knees was present moderately only on active motion (++), and there was only minimal residual pain in the right shoulder, hand, and right wrist (+). The sedimentation rate at this time remained elevated (28 mm., uncorrected 26). On the ninth day the sedimentation rate had fallen to normal (5 mm.). At this time he was walking normally without his cane, and except for slight residual stiffness in the joints was free of signs and symptoms of rheumatoid arthritis (Grade 1 response). No significant changes occurred in the laboratory findings during cortisone therapy, and the glucose tolerance curve showed hypoglycaemic levels after $2\frac{1}{2}$ hours (fasting, 87 mg.; $\frac{1}{2}$ hr, 144; 1 hr, 126; $2\frac{1}{2}$ hrs, 47). The patient was now working 12 hours daily in his store and walking several miles without pain.

* With regard to glucocorticoid excretion levels in chronic rheumatoid arthritis, Venning and others (1951) found the average excretion levels to be considerably lower than normal, but three cases with acute onset had increased glucocorticoid excretion.

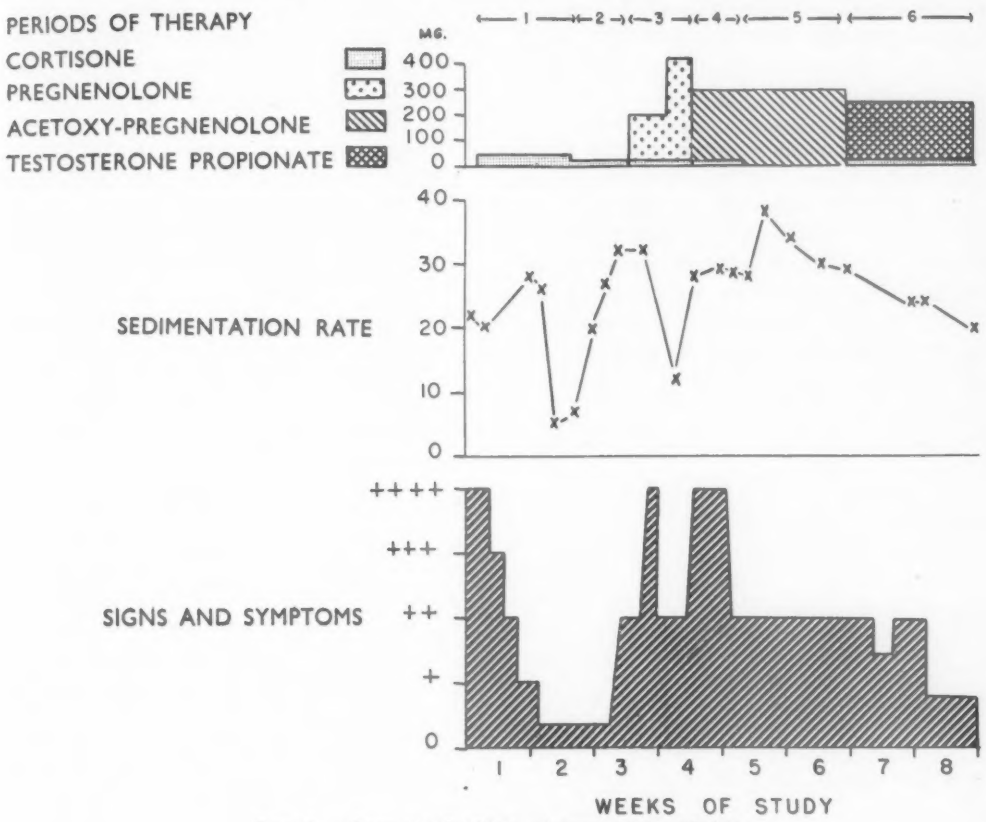

FIG. 2.—Case 2 (C.5296), rheumatoid arthritis.

Periods of therapy:

(1) Disease controlled on cortisone acetate 50 mg./24 hrs.
(2) Cortisone 25 mg./24 hrs. Minimal disease activity.
(3) Simultaneous administration of pregnenolone 200 and 400 mg./24 hrs. Severe exacerbation.
(4) Simultaneous administration of acetoxypregnenolone 300 mg./24 hrs. No beneficial effect.
(5) Cortisone discontinued and acetoxypregnenolone continued. No beneficial effect.
(6) Cortisone 25 mg./24 hrs and testosterone propionate 250 mg./24 hrs. Some improvement, but remission not achieved.

Fig. 2 (2). To find whether the failure of response to testosterone, DOCA, and ascorbic acid was due to the severity of the rheumatoid arthritis, the dose of cortisone was reduced to 25 mg./24 hrs. On the 3rd day of this reduced dosage there was a mild return of signs and symptoms, and the sedimentation rate rose to 20 mm. (uncorrected 13), and on the sixth day to 30 mm. (uncorrected 28). At this time there was moderate pain, swelling, tenderness, and heat in the right knee and both heels which prevented walking except with a cane, but other joints previously involved were symptomless, and the patient found it necessary to take analgesics only twice daily. The disease activity was now considered moderate, ++ (Grade 3 response).

Fig. 2 (3). To find whether other steroids were capable of reversing this minimal degree of disease activity, cortisone 25 mg./24 hrs was continued, with the addition of pregnenolone intramuscularly 200 mg./24 hrs for 5 days. The sedimentation rate fell from 32 mm. to 12 mm., but the joint pain and swelling became greatly aggravated, so that the patient was unable to walk. The dose of pregnenolone was then increased to 400 mg./24 hrs

(in combination with cortisone 25 mg./24 hrs) for 3 more days, after which the sedimentation rate had risen to 28 mm., and the joint swelling, pain, and inflammation had become more severe than pre-treatment. The patient was now bed-ridden or brought to the clinic in a wheel chair, ++++ (Grade 4 response), and his condition was worse than when maintained on cortisone 25 mg./24 hrs alone.

Fig. 2 (4). Acetoxypregnenolone in aqueous crystalline suspension intramuscularly 300 mg./24 hrs was substituted for pregnenolone, and given in combination with cortisone 25 mg./24 hrs. The sedimentation rate continued to rise until on the 10th day it was 38 mm. (uncorrected 43), but the patient's clinical condition, was the same as on cortisone 25 mg./24 hrs alone. There was fluid, heat, and redness in the right knee and ankle, and moderate pain on active movement (++).

Fig. 2 (5). When cortisone was stopped and acetoxypregnenolone 300 mg./24 hrs continued there was no detectable change either in sedimentation rate or in signs and symptoms. No significant changes occurred in other laboratory findings, and the glucose tolerance curve remained as pre-treatment. On the 22nd day of acetoxypregnenolone therapy the patient's condition was unchanged and the sedimentation rate remained abnormally elevated at 31 mm.

Treatment was then withdrawn for a 10-day period without change in signs and symptoms or sedimentation rate.

Fig. 2 (6). Testosterone propionate 250 mg./24 hrs intramuscularly was then given with cortisone 25 mg./24 hrs. There was subjective and objective improvement, the patient being able to walk without his cane and having only slight pain in the right knee, but the sedimentation rate remained elevated (20 mm.).

Injections of distilled water were then substituted for one week, on the fifth day of which the sedimentation rate had risen to 26 mm. (uncorrected 38) with a return of severe pain and swelling in knee and ankle joints (+++).

At this time cortisone acetate 50 mg./24 hrs was given, and after 2 weeks on this dose the patient was symptom-free, and the sedimentation rate had returned to normal (10 mm., uncorrected 12), with only slight residual pain in the wrists and ankles on strenuous activity.

After three weeks of this minimal effective dose a placebo was substituted, and in one week signs and symptoms returned, with moderately severe swelling and inflammation in ankles and knee joints and elevation of the sedimentation rate to 26 mm.

Testosterone 250 mg. with cortisone 25 mg./24 hrs was thus not as effective as cortisone 50 mg./24 hrs alone. The latter caused complete remission, and the former only slight improvement without reduction in the sedimentation rate. The minimal degree of disease activity was not reversed by pregnenolone, acetoxypregnenolone, or testosterone.

Case 3 (F.2619, see Fig. 3).—48-year-old white male, with rheumatoid arthritis of 13 years' duration.

Disease Activity.—The disease has slowly progressed to involve the joints of the hands, wrists, elbows, ankles, feet, and knees with typical deformities in the hands, including subluxation of the proximal interphalangeal joints. There was bony ankylosis of both wrists and acute inflammatory signs and symptoms in all the involved joints, especially in the elbows, shoulders, and knees, which prevented all activity except minimal self care.

History.—Other pertinent features of this case were the occurrence of hyperthyroidism with thyroidectomy performed 3 years after the onset of rheumatoid arthritis. No improvement in the arthritic signs and symptoms had followed, but subsequently there had been onset of exophthalmos of a non-progressive type. The basal metabolism rate had since remained within normal limits. Amongst the laboratory findings was a disturbed carbohydrate regulation with decreased glucose tolerance to be discussed later. The patient also had a history of gastric ulcer for which a subtotal gastrectomy had been

performed in 1947. There were dark, pigmented, yellowish-brown areas, especially on the face and elbow, but no pigmentation of the buccal mucosa.

Laboratory Findings.—Blood pressure 128/86.
Serum electrolyte normal range.
Red blood count 3,000,000, normal differential.
Abnormally low urinary 17-ketosteroid excretion of 3·4 mg./24 hrs; gonadotropins—abnormally high, positive at a 105/24 hrs.
During a 5-year pre-treatment period, the sedimentation rate had remained abnormally elevated (14 to 20 mm.), and the arthritic signs and symptoms in the involved joints had remained active during this period.

Assessment.—At the beginning of treatment, the degree of disease activity was ++++, and the patient was classified as " Stage 4, active, Class 3 ".

Therapy.—He was placed on testosterone propionate in oil solution intramuscularly 250 mg. twice a week. After the second injection there was immediate objective and subjective improvement, arthritis activity decreasing to ++ with improved movement of all involved joints and decrease of pain to moderate. During the third week of therapy, the pain and arthritis signs and symptoms returned to pre-treatment levels, but by the end of the week there was cessation of all pain, and free movement in joints where there was no fibrous or bony ankylosis. The sedimentation rate had now fallen from 20 mm. (uncorrected 39) to 11 mm. (uncorrected 13), and remained essentially normal during the fourth and fifth weeks of therapy. The patient felt stronger, was almost entirely free from pain, and expressed a desire to return to work. This may be classified as Grade 2 response. There was a 6½-lb. weight gain during testosterone therapy. There was, however, no change in laboratory findings, the glucose tolerance curve before treatment was fasting, 90 mg.; ½ hr, 213; 1 hr, 288; 1½ hr, 258; 2 hrs, 140; 2½ hrs, 80 mg. After the fifth week of testosterone therapy the curve was fasting, 99 mg.; ½ hr, 238; 1 hr, 266; 1½ hrs, 107; 2½ hrs, 35. Thus there was essentially no change, there being an elevated plateau 1-1½ hours, and hypoglycaemic levels at 2½ and 3½ hours, both before and after treatment. There was no change in the exophthalmos during testosterone therapy; nor in the elevated gonadotropins, which remained positive at 105 glycogenic units/24 hrs.

To determine the effects of desoxycorticosterone acetate on the decreased glucose tolerance and on the arthritis signs and symptoms, DOCA intramuscularly 10 mg./24 hrs was given for one week, during the last 3 days of which 1 g. ascorbic acid intravenously was given simultaneously. During this week there was no change in signs or symptoms as compared with the pre-treatment period. The sedimentation rate remained normal as during testosterone therapy (9 mm., uncorrected 30). The glucose tolerance was increased, but not above the usual range of variability of this test: fasting, 85 mg.; ½ hr, 190; 1 hr, 184; 2 hrs, 95; 2½ hrs, 53. After a one-week control period a combined glucose-insulin tolerance test showed a return to decreased glucose-insulin tolerance and also insulin resistance, fasting, 87 mg.; ½ hr, 225; 1 hr, 219; 2 hrs, 95; 3 hrs, 53. At this time the disease activity of rheumatoid arthritis had returned to ++++, with severe pain and swelling in the right knee preventing walking. Severe pain also recurred in the left shoulder and proximal interphalangeal joints of the left hand.

Fig. 3 (1). Cortisone acetate 100 mg./24 hrs was given intramuscularly. At the beginning of therapy the sedimentation rate was elevated (14 mm., uncorrected 33). After 3 days there was no change in signs and symptoms, the patient could not sleep because of pain requiring frequent analgesics, and was unable to stay on his feet on account of pain in the knees and weakness. On the fourth day, however, arthritis activity had fallen to + with only minimal pain in the right knee, and shoulder joints, and left hand. Swelling in the right knee had markedly diminished and by the fifth day was barely detectable. On the ninth day the sedimentation rate had fallen to normal (0 mm., uncorrected 14). The left hand which had been immobile, fixed in a grasping position, was now mobile with little

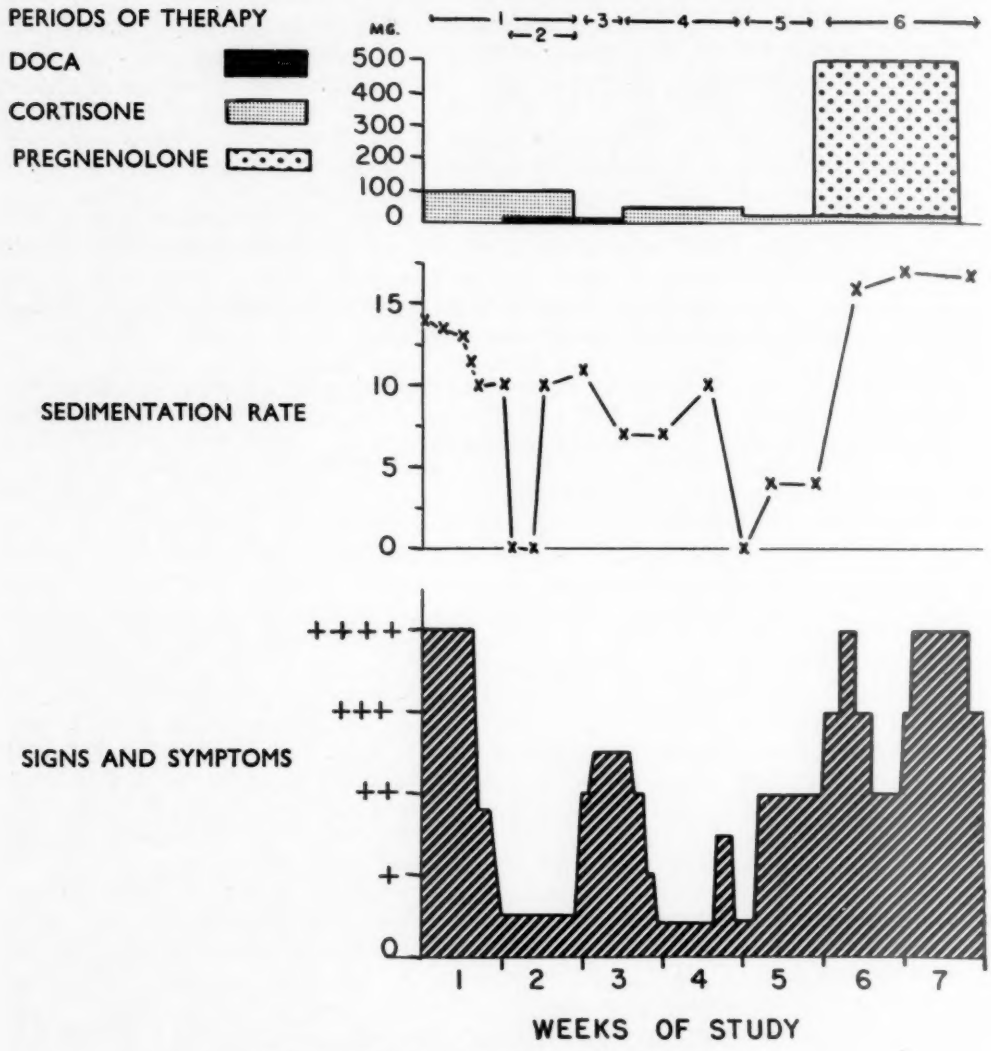

FIG. 3.—Case 3 (F.2619), rheumatoid arthritis.

Periods of therapy:

(1) Disease controlled on cortisone acetate 100 mg./24 hrs.
(2) Simultaneous administration of DOCA 10 mg. No effect.
(3) Cortisone discontinued. DOCA continued. Immediate exacerbation.
(4) Disease controlled on cortisone 50 mg./24 hrs. Minimum effective dose.
(5) Mild exacerbation on cortisone 25 mg./24 hrs. Minimal disease activity.
(6) Simultaneous administration of pregnenolone 500 mg./24 hrs. No beneficial effect.

residual stiffness. There was no pain or tenderness in any of the involved joints. On the tenth day the patient contracted a severe head cold and bronchitis with purulent sputum and was put on 1 g. sulphadiazine 4-hourly, but there was no return of signs or symptoms of arthritis.

Fig. 3 (3). During the third week, to find whether desoxycorticosterone acetate would prevent a remission caused by cortisone, DOCA 10 mg./24 hrs intramuscularly was given simultaneously with cortisone 100 mg./24 hrs, after which there was no elevation of the sedimentation rate, which remained normal at 10 mm. (uncorrected 35), and no return of

signs and symptoms of arthritis. The patient was now able to walk vigorously and had only occasional twinges of pain in knee and elbow.

Fig. 3 (3). Cortisone was now stopped and DOCA 10 mg./24 hrs intramuscularly continued. On the second day after the withdrawal of cortisone the signs and symptoms of arthritis recurred, pains were severe, and both elbows became very swollen with large nodules approximately 4 cm. in diameter on the dorsal surfaces. The arthritic activity was now +++ in the involved joints, but the sedimentation rate remained normal (7 mm., uncorrected 28).

Fig. 3 (4). Because of this severe exacerbation DOCA was stopped on the third day and cortisone 50 mg./24 hrs begun. On the second day pains and swelling in the involved joints were markedly diminished, and they had disappeared by the third, fourth, and fifth day. During an additional week of cortisone 50 mg./24 hrs there was occasional pain requiring analgesics, and lasting on one occasion 8 to 12 hours. The patient became completely symptom-free after 4 weeks on cortisone 50 mg./24 hrs, and the sedimentation rate was normal (0 mm., uncorrected 15).

Fig. 3 (5). The dose of cortisone was further reduced to 25 mg./24 hrs, but on the third day arthritis activity had risen to ++ with a return of swelling and nodules in both elbows and moderate pain in the other involved joints. After one week of this reduced cortisone dosage, the disease activity remained constant at ++ with only moderate changes in the involved joints and minimal swelling. The patient was able to resume his activities, walked vigorously, and had a good appetite, with no systemic signs of arthritis. The sedimentation rate remained normal (8 mm., uncorrected 24). This was considered a minimal disease activity on cortisone 25 mg./24 hrs.

Fig. 3 (6). Pregnenolone crystalline aqueous suspension 500 mg./24 hrs was given with cortisone 25 mg./24 hrs to see whether this state of minimal disease activity would be reversed. On the second day of combined pregnenolone cortisone therapy, the signs and symptoms had returned to ++++ with severe exacerbation of pain, swelling in all the involved joints, and marked involvement of the left wrist, +++. Severe pain prevented the patient from eating or sleeping normally and large amounts of analgesics were required (12 analgesic tablets per day). The exacerbation of signs and symptoms varied from ++ to ++++ during this combined pregnenolone/cortisone therapy, but there was continuous pain requiring analgesics. The sedimentation rate remained elevated (16 mm., uncorrected 26). Severe pain in all the involved joints and marked swelling persisted through the second week of combined therapy and the patient was objectively and subjectively worse than when receiving cortisone alone (Grade 4 response).

Testosterone propionate in oil solution 200 mg./24 hrs intramuscularly was now substituted for pregnenolone/cortisone. Despite the decline of the sedimentation rate to normal values (first week 12, uncorrected 30; second week 10, uncorrected 25), the arthritic activity remained at ++++ during the first week, and +++ during the second week, with severe pain in all involved joints. The patient was unable to walk, dress or care for himself because of pain and swelling in the knee, large subcutaneous nodules in both elbows with swelling, and marked swelling and pain in the left wrist. Frequent analgesics were necessary because of the severe pain, and the patient required a wheel chair for the first time. Thus there was Grade 4 response to testosterone, with no detectable effect on the minimal disease state, although a reduction occurred in the sedimentation rate.

When testosterone was discontinued and cortisone increased to 50 mg./24 hrs, the signs and symptoms gradually diminished until there was only minimal residual pain, swelling, and stiffness in the involved joints, i.e. +arthritic activity. The sedimentation rate was normal (10 mm., uncorrected 31), and the major signs of inflammation resolved; thus there was Grade 2 response after one week on cortisone 50 mg./24 hrs, which can thus be taken as the minimum effective dose.

Thus cortisone 50 mg./24 hrs for one week rendered the patient symptom free, whereas other steroids in combination with cortisone 25 mg./24 hrs brought on a severe

exacerbation of signs and symptoms. During a subsequent 4-week period on cortisone 50 mg./24 hrs the patient remained symptom-free except for a flare-up in the 5th carpal-metacarpal joints, where there was acute inflammation, pain, redness, and swelling lasting for 3 days.

After 5 weeks the dose of cortisone was changed from 50 mg./24 hrs to 100 mg. every other day with no return of signs and symptoms or rise in sedimentation rate. After 10 weeks, except for an occasional flare-up in the joints lasting one or two days, the patient could be considered in complete remission.

When cortisone was withdrawn exacerbation occurred within one week, and during the second week the sedimentation rate returned to normal levels.

After 10 weeks on cortisone there was no change in weight, blood pressure, glucose tolerance, 17-ketosteroid excretion, or serum electrolyte levels.

More recently the same patient has been maintained on a crystalline suspension of cortisone acetate orally for 12 weeks. The cortisone is taken four times daily and approximately one-third more is required than by the intramuscular route. Methyl testosterone 25 mg./24 hrs orally was added when the patient complained of extreme weakness and malaise. The serum potassium at this time was 14·3 mg. per cent. (normal 17-21 mg. per cent.), and the symptoms diminished within one week with gain in strength and appetite. It is further suggested that potassium chloride 4-6 mg./24 hrs orally, should supplement the dietary potassium intake.

Case 4.—38-year-old male, with psoriasis of 10 years' duration and rheumatoid arthritis for 1 year during which there had been no remission (psoriatic arthritis).

Disease Activity.—The arthritis first involved the wrist and ankle joints, slowly progressing to the shoulders and elbow joints. There were typical *x*-ray changes in the wrists and feet with juxta-articular osteoporosis, and narrowing of the joint spaces, but no ankylosis. The sedimentation rate was consistently elevated, from 31 mm. (uncorrected 45) to 37 mm. (uncorrected 51).

History.—Previous therapy with gold had had no effect, and there had been a 30-lb. weight loss in 6 months. Treatment with ACTH prior to the present study had resulted in only slight improvement in the arthritis, with aggravation of the psoriasis which spread to involve the entire trunk, and upon withdrawal of ACTH there had been exacerbation of the rheumatoid arthritis.

Assessment.—The ankles were severely painful and swollen (+++) preventing walking, and pain, stiffness, and swelling in the left wrist, elbow, and shoulder joints limited his activities to minimal self care. The patient was classified as " Stage 3, active, class 3 ".

Therapy.—The patient was placed on testosterone propionate intramuscularly, two injections per week. After the first injection (300 mg.) pain and swelling in ankles markedly diminished for 24 hours, and after the second injection (250 mg.) the psoriasis was objectively and subjectively improved. During the second week he received two injections of 500 mg. testosterone propionate intramuscularly, after the first of which the left wrist was symptom-free for 24 hours, and the left ankle and heel were free from pain for 3 days. After the second injection of 500 mg., there was a similar improvement which was maintained during the third week on 500 mg. twice weekly. After the 3rd week the sedimentation rate had declined to 14 mm. (uncorrected 21); the patient was walking well, and had only minimal pain and swelling in ankles, wrists, and feet. The psoriasis had entirely disappeared from the trunk and was greatly improved elsewhere, and he was making plans to return to work. From the fourth to the seventh week on 500 mg. twice weekly this improvement was maintained (Grade 2 response). The patient was now at work, and had no pain, swelling, or stiffness in the joints, and only some vasomotor symptoms (weakness and sweating). He now found it necessary to shave twice a day, whereas previously once every day or every other day was sufficient. The contrast with his

condition before treatment (crippled and unable to care for himself, and complaining " that he was dying a slow death ") as compared with the alert, vigorous person who had now returned to his job as salesman after treatment with testosterone propionate was remarkable. During the eighth and final week the dosage was increased to 500 mg. three times. The sedimentation rate had now fallen to normal (10 mm., uncorrected 18), and the patient was entirely symptom-free. There had also been a 15-lb. weight gain during the 8 weeks (Grade 1 response). Two weeks after discontinuing the testosterone, there was a return of minimal pain in the wrist and ankles, and the sedimentation rate rose to 20 mm. (uncorrected 22). Six weeks later, the articular pain and swelling had increased in the ankles and wrist (++), and weakness and vasomotor symptoms prevented the patient from working. The sedimentation rate was abnormally elevated (18 mm., uncorrected 19), and there was also a 12-lb. weight loss since the withdrawal of testosterone.

450 mg. testosterone propionate in aqueous macrocrystalline suspension* was now started. For 10 days after a single injection there was a remission in the articular signs and symptoms and the patient returned to his job. After one week the sedimentation rate had returned to normal (7 mm., uncorrected 9) (Grade 1 response). After this single injection of testosterone propionate, the 17-ketosteroid excretion rose to 38·4 mg./24 hrs on the 1st day, gradually falling to 21·6 mg./24 hrs on the sixth, 12·2 mg./24 hrs on the seventh, and 11·9 mg./24 hrs on the eleventh day, the last value being within the pre-injection range. Coinciding with the return of the 17-ketosteroids to pre-injection levels, there was an exacerbation of arthritic signs and symptoms.

Results

The administration of pregnenolone, acetoxypregnenolone, and testosterone in large doses to five patients in the minimal disease state of rheumatoid arthritis failed to reverse this delicate balance. The erythrocyte sedimentation rate remained abnormally elevated, and the arthritis signs and symptoms were not perceptibly affected. The addition intramuscularly of 25 mg. cortisone acetate per 24 hours, was sufficient to reverse the minimal disease state of rheumatoid arthritis in the patients studied, the sedimentation rate falling to normal, and the disease becoming asymptomatic, with complete disappearance of articular inflammation. This reversal occurred within 7 days, yet neither 400 to 500 mg. pregnenolone intramuscularly per 24 hours for 21 days, 300 to 500 mg. acetoxypregnenolone intramuscularly per 24 hours for 14 days, nor 250 mg. of testosteronepropionate intramuscularly per 24 hours for 14 days, was able to produce the anti-rheumatic effect of the 25-mg. increment of cortisone. These preliminary studies of pregnenolone, acetoxy-pregnenolone, and testosterone, show that if they have any anti-rheumatic activity at all it is less than 10 per cent. of that of cortisone.

A method has thus been developed for expressing the activity of unknown steroids as a percentage of the anti-rheumatic activity of cortisone. So far, none of the hormones studied by the method of " cortisone comparison ", appeared to have any anti-rheumatic activity at all.

In a separate series of three patients, two underwent dramatic remission while on testosterone therapy, and a third markedly improved, the erythrocyte sedimentation rate becoming normal and signs and symptoms disappearing (Grade 1 improvement). These patients fulfilled the criteria outlined on page 235,

* Ciba preparation of testosterone large crystal suspension.

having been observed for 2 to 10 years, during which time there had been no remission and the erythrocyte sedimentation rate had remained abnormally elevated, except for occasional normal values. In all the patients studied with testosterone therapy, the sedimentation rate was lowered independently of the disease activity, and in all the patients who showed no response to testosterone, there was subsequent remission on cortisone therapy, though while in a state of minimal disease activity, they showed no improvement when testosterone was added to the cortisone. It is therefore possible that variants exist in the types of rheumatoid arthritis, some of which respond to certain steroids but not to others.

Summary and Conclusions

Methods of eliminating significant variables encountered in research in rheumatoid disease are outlined.

A method is described of eliminating one important variable—the severity or degree of activity of the disease. The patient is given the *maximum ineffective* dose of cortisone (which maintains him with minimal disease activity), and then sufficient cortisone to cause remission is added, so that the exact amount necessary to maintain remission is known.

New untested steroids are administered to these patients with minimal disease activity, and if any anti-rheumatic activity is observed, it can be quantitatively equated with the anti-rheumatic activity of cortisone.

When pregnenolone, acetoxypregnenolone, and testosterone were studied by this method it was found that any anti-rheumatic activity of these three steroids in rheumatoid arthritis was less than 10 per cent. of the activity of cortisone and was not observable clinically. An increment of 25 mg. cortisone acetate intramuscularly per 24 hours, in place of the test steroid, caused the disappearance of the signs and symptoms of rheumatoid arthritis and normalized the sedimentation rate within 7 days.

It is suggested that the effect of testosterone in rheumatoid arthritis needs further study. A remission (Grade 1 response) was observed in two patients treated with testosterone under controlled conditions, but no effect (Grade 4) was perceptible in other patients in whom a remission (Grade 1) was afterwards seen on cortisone therapy.

This method of testing steroids in terms of " cortisone activity " by reversal of the " minimum disease state " lends itself to the investigation of the anti-rheumatic activity of other steroids yet to be tried. This and the other methods set forth may be applied to any field of clinical research, but are especially useful in the study of the rheumatic disease.

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Activité Anti-rhumatismale de Plusieurs Stéroïdes

RÉSUMÉ ET CONCLUSIONS

L'auteur esquisse les méthodes d'élimination de variables importantes rencontrées dans les recherches sur l'arthrite rhumatismale.

Une méthode, conçue afin d'éliminer la variabilité déterminée par la gravité et par le degré d'activité de l'arthrite rhumatismale, consiste à administrer *la dose inefficace maxima* de cortisone (maintenant le malade en état d'activité morbide minime). La dose additionnelle de cortisone, nécessaire pour produire le rétablissement du malade, sert d'étalon pour les autres substances capables de produire le même effet.

L'activité anti-rheumatismale de la testostérone, de la pregnénolone, et de l'acétoxypregnénolone, étudiée par cette méthode, se montra inférieure à 10% et ne porta pas sur les signes cliniques. La dose supplémentaire de 25 mg. d'acétate de cortisone par voie intramusculaire par 24 heures fit disparaître les signes de l'arthrite rhumatismale et ramena la vitesse de la sédimentation globulaire à la normale en moins de 7 jours.

L'effet de la testostérone dans l'arthrite rhumatismale demande des études ultérieures. Un rétablissement (amélioration du premier degré) fut observé chez deux malades traités par la testostérone dans des conditions contrôlées, mais aucun effet (du quatrième degré) ne fut observé chez d'autres malades chez qui, plus tard, on obtint un rétablissement (du premier degré) avec la cortisone.

Cette méthode d'étalonnage des stéroïdes en fonction d'activité de la cortisone par inversion de " l'état morbide minime " se prête aux recherches sur l'activité anti-rhumatismale des autres stéroïdes pas encore soumises à l'épreuve. Celle-ci, ainsi que d'autres méthodes destinées à contrôler les variables, mentionnées ci-dessus, peuvent s'appliquer à n'importe quelle recherche clinique, mais elles sont particulièrement utiles dans l'étude de l'arthrite rhumatismale.

Actividad Antirreumática de Ciertos Esteroides

RESUMEN Y CONCLUSIONES

El autor reseña los métodos de eliminación de variables significativas encontradas en las investigaciones acerca de la artritis reumatoide.

Un método, concebido para eliminar la variabilidad debida a la gravedad y al grado de actividad de la artritis reumatoide, consiste en administrar *la dosis ineficaz maxima* de cortisona (manteniendo el enfermo en el estado de actividad mórbida mínima). La dosis adicional de cortisona necesaria para producir el restablecimiento del enfermo sirve de patrón para las otras substancias experimentales, destinadas a producir el mismo efecto.

La actividad antirreumática de la testosterona, de la pregnenolona, y de l'acetoxypregnenolona, estudiada por este método, se mostro inferior à 10% y sin influencia sobre los signos clínicos. La dosis suplementaria de 25 mg. de acetato de cortisona por vía intramuscular administrada por 24 horas hizo desaparecer los signos de la artritis reumatoide y normalizó la sedimentación globular en menos de 7 dias.

El efecto de la testosterona sobre la artritis reumatoide demanda estudios ulteriores. El restablecimiento (mejoría de primer grado) fué observado en el caso de dos enfermos tratados con testosterona en condiciones controladas, pero ningún efecto palpable (de cuarto grado) se pudo observar en otros enfermos en los cuales se obtuvo posteriormente restablecimiento (de primer grado) con cortisona.

Este método de valuación de los esteroides en función de la actividad de la cortisona, por reversión del " estado mórbido mínimo " se presta para investigar la actividad antirreumática de otros esteroides aún no comprobados. Este, así como otros métodos, mencionados arriba, concebidos para controlar los variables, se pueden aplicar a cualquier otra investigación clínica, pero son particularmente útiles en el estudio de la artritis reumatoide.

AMYLOIDOSIS IN STILL'S DISEASE

BY

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Still (1897) first described the form of chronic polyarthritis of childhood now associated with his name, and six years later Whitman (1903) described two such cases complicated by amyloidosis, but since then few cases with *post-mortem* findings have been reported. Portis (1938) gave the findings in two fatal cases of Still's disease with amyloidosis, and was able to find five further cases among twelve *post-mortem* accounts in the literature. Trasoff and others (1944), in a review of the literature, collected 31 cases of amyloidosis in rheumatoid arthritis (nine below 16 years of age), all but five of which are known to have died. They also described a case of a patient suffering from Still's disease with amyloidosis who recovered, and they quote a similar case from Kennedy (1935). Further cases of this combination of diseases are recorded from the Massachusetts General Hospital (1945), by Coss and Boots (1946), and by Pickard (1947).

Dahlin (1949) has recently given an account of the pathology of amyloidosis. Amyloid disease complicating rheumatoid arthritis and Still's disease is of secondary type (Reimann and others, 1935) affecting mainly the kidneys, liver and spleen.

The case presented below is one of Still's disease of severe nature, with gross pericarditis and complicated by amyloidosis.

Case Report

The patient, a boy aged 3 years and 10 months, was admitted to hospital in February, 1947, with a recurrent polyarthritis of 3 months' duration. He had had whooping-cough at 3 years and 6 months, but had otherwise been quite well, and there was no history of family illness, save for rheumatic fever in an uncle and two cousins. The present illness had the following features: There was a painful, flitting polyarthritis, particularly of the knees, wrists, ankles, and cervical spine, associated with severe general symptoms, notably anorexia, intermittent pyrexia to 102° F. (38·9° C.), lymphatic gland enlargement, normochromic anaemia, and a markedly raised sedimentation rate. A week after admission a pericardial rub was heard, the heart having previously been clinically normal. The rub disappeared in a few days, but recurred 3 weeks and 5 weeks later, when it was heard for several days. At this period the child was very ill, with marked orthopnoea, and was obviously deteriorating, and he was taken home by his parents against medical advice, after 7 weeks in hospital. There had been no clinical response to aspirin in adequate dosage.

X ray of the chest showed general enlargement of the heart shadow; an electrocardiogram (leads I, II, and III) was normal; T.3 was inverted. There was slight proteinuria with no casts. *X* ray of the joints showed periarticular soft tissue thickening without alteration in the joint spaces.

He was admitted to another hospital six weeks later with flexion contractures of the hips and knees, and intermittent pyrexia and anaemia. The heart was now clinically normal, and the liver and spleen were not palpable. Two weeks after admission a recurrence of the pericardial rub was noted with an apex beat in the anterior axillary line and a pulse of 140-160. This was a transitory incident, however, and he again improved a little. In view of the severe anaemia he was transfused with stored blood, his haemoglobin rising from 39 to 64 per cent. (Haldane). The limbs were splinted and a course of calciferol was given (50,000 international units *bis die* for 1 month), with no effect other than the production of a high blood calcium level of 13 mg./100 ml. He was discharged unimproved in October, 1947.

Investigations.—Red blood count 2·8 million per c.mm.
Haemoglobin 39 per cent. (Haldane).
White blood count 24,100 (Polymorphs 21,700).
There were several white blood counts of approximately this figure during his illness. The urine contained a trace of protein and a few cellular and hyaline casts. Radiography demonstrated osteoporosis and delayed ossification of the carpal and tarsal bones with enlargement of the epiphyses.

He was re-admitted to hospital at the age of 5, his condition having apparently remained unchanged for 5 months since his most recent discharge from hospital. Five weeks previously, however, after a crop of styes, he had developed diarrhoea and vomiting, and then swelling of the legs and abdomen. On admission he was found to have ascites, a greatly enlarged liver, and oedema of the legs, scrotum, and lumbosacral region.

The heart was enlarged, with an apical systolic murmur. Lymphatic glands were palpable in both axillae and in the neck, and the spleen was palpable. He was now found to have developed gross proteinuria with some hyaline casts. There was severe hypochromic anaemia: plasma proteins 4·15 g. per 100 ml. (fibrinogen 0·33, albumin 2·86, and globulin 0·96 g. per 100 ml.) An electrocardiogram again showed an inversion of T.3.

High protein diet and blood transfusion were given with subsequent disappearance of oedema and ascites, but he developed a severe attack of varicella, became oedematous again, and died 18 months after the onset of his illness.

***Post-Mortem* Examination.**—This confirmed the presence of marked periarticular thickening of many joints. The heart weighed $4\frac{3}{4}$ oz. (135 g.); there was no evidence of valvular disease; the pericardial sac was obliterated by fibrous adhesions. The liver was greatly enlarged, weighing 3 lb. 10 oz. (1,644 g.); the spleen, weighing 5 oz. (142 g.) was bound down by adhesions. The kidneys weighed 7 oz. (198 g.) each; the capsules stripped easily.

Microscopic Examination.—This demonstrated diffuse amyloidosis and fatty change in the liver, deposits of amyloid in the Malpighian bodies and around the vessels of the spleen, and large deposits of amyloid in all the glomerular tufts of both kidneys (Figs 1 and 2, overleaf). Section of the mitral valve was normal: there were no Aschoff nodules, but some of the heart muscle fibres were indistinct and appeared to be infiltrated with amyloid.

FIG. 1.—Kidney. Infiltration of glomeruli with amyloid. Methyl violet (×200).

Discussion

This case exemplified most of the classical features of Still's disease, notably a chronic polyarthritis affecting the larger rather than smaller joints with periarticular thickening, enlargement of the lymph nodes, anaemia, and bouts of fever. Marked polymorphonuclear leucocytosis was noted on several occasions. Recurrent clinical pericarditis of a severe nature was a feature of this case, confirmed at

FIG. 2.—Spleen. Infiltration of Malpighian bodies with amyloid. Methyl violet (× 100).

autopsy by an adherent pericardium. The three original cases of Still which came to autopsy each had an adherent pericardium, but pericarditis had not been noted clinically. The development of amyloid disease was suggested by gross hepatic enlargement, marked proteinuria, and oedema, though the congo red test was not performed. There was hypoproteinaemia without increase in the plasma globulin. Death appeared finally to be due to circulatory failure rather than

uraemia, which is the usual cause of death from this type of secondary amyloidosis. Blood urea estimations had not, however, been carried out.

It is difficult to assess the incidence of this complication of Still's disease, but it is not common and follows only the more severe forms of the disease. Lush and others (1948) found one case of amyloidosis in 200 cases of rheumatoid arthritis of all ages; Pickard (1947) reports one death from amyloid disease in 35 cases of rheumatoid arthritis in children; Edström (1947) makes no mention of this complication in a review of 65 cases of juvenile rheumatoid arthritis in Sweden. The papers of Portis (1938) and of Trasoff and others (1944) suggest, however, that where Still's disease brings about death, amyloidosis is often the determining factor.

Jennings (1950) states that in the past 20 years enough cases of amyloidosis with rheumatoid arthritis have been described to suggest that this complication of rheumatic and rheumatoid disease will be recognized more often if it is always suspected when the condition lasts for more than one year and is associated with emaciation and anaemia, as in our case. Early diagnosis is of importance if the effect of liver or other therapy is to be assessed and gingival biopsy may be a simple and easy method of demonstrating amyloid tissue (Selikoff and others, 1949).

Summary

A case of Still's disease complicated by clinically recognized pericarditis and by amyloidosis is described. The *post-mortem* findings are summarized.

Our thanks are due to Prof. C. Bruce Perry and to Dr. J. Apley for permission to publish this case, and to Dr. Apley for his advice and criticism. The *post-mortem* and histological reports were made by Dr. H. J. Heathcote.

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Dégénérescence Amyloïde dans la Maladie de Still

RÉSUMÉ

On décrit un cas de maladie de Still, compliquée de péricardite reconnue en clinique et de dégénérescence amyloïde. On présente un résumé des résultats d'autopsie.

Amiloidosis en la Enfermedad de Still

SUMARIO

Se describe un caso de la enfermedad de Still complicado con pericarditis y con amiloidosis, clínicamente reconocidas. Se presenta un resumen de los resultados de autopsia.

RESPONSE OF SCHOENLEIN-HENOCH SYNDROME TO ACTH*

REPORT OF A CASE WITH SERIAL SKIN BIOPSIES

BY

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The Schoenlein-Henoch syndrome, a condition of unknown aetiology, is defined as the clinical combination of gastro-intestinal symptoms, articular symptoms, and a characteristic exanthema which is usually purpuric. Nephritis may be an associated finding. The few available histological studies stress inflammation of the minute vessels as the dominant pathological feature (Gairdner, 1948). Because of the similarity of these manifestations of systemic disease to those of rheumatic fever, disseminated lupus erythematosus, polyarteritis nodosa, and serum sickness, it was of interest to note whether ACTH would effect as striking symptomatic relief in the Schoenlein-Henoch syndrome as it does in these clinically similar conditions.

In the present study, ACTH was employed in the treatment of a case with the classical features of the Schoenlein-Henoch syndrome, including nephritis. Although the administration of ACTH was followed by symptomatic improvement, exacerbations occurred after the cessation of each course of therapy, and he nephritis persisted. The study of seven serial skin biopsies afforded the opportunity of observing what, if any, histological changes took place in consequence of ACTH therapy.

Case Report

Clinical History.—M.B., a 15-year-old schoolgirl, was admitted to the Massachusetts General Hospital on May 11, 1950, complaining of malaise, severe anorexia, joint pains, and a rash. She had been well and gave no history of infection or drug administration preceding the appearance of a pruritic maculopapular exanthema on the dorsum of the ankles and the extensor surfaces of the elbows and wrists 5 weeks previously. The rash extended progressively up the legs to the knees, thighs, and buttocks. Some of the maculopapular lesions on the extensor surfaces of the lower legs became haemorrhagic bullae, then dried and became scabbed. Simultaneously with the appearance of the exanthema, she had developed malaise, severe anorexia, and generalized abdominal pain which tended to localize in the right iliac fossa. Appendectomy had been performed at another hospital on April 12, 1950, several days after the onset of these symptoms. The surgeon reported a " subacute appendix " though no histological examination was made. Colicky pain accompanied by vomiting had persisted intermittently after the operation. Two and a half weeks after the onset of symptoms, the knees, elbows, and

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wrists became painful, and painless swelling of the ankles developed. The patient was therefore admitted to the hospital. She had lost 18 lb. in weight since her illness began.

The past history and family history were irrelevant.

Physical Examination.—The patient appeared thin, pale, and ill, but in no acute distress. The rectal temperature was 100·2° F.; pulse 110 per minute; blood pressure 160/120. The lower eyelids were slightly puffy and the dorsum of the feet and ankles showed slight pitting oedema. The abdomen was not tender. The liver was palpable one fingerbreadth below the right costal margin and was firm. The spleen was palpable two fingers-breadth below the left costal margin. No abnormalities were noted on examination of heart, lungs, fundi, and central nervous system. Both knee joints exhibited slight soft tissue thickening and small effusions. Movements of the elbows were painful. On the extensor surfaces of the lower legs there were numerous lesions of the following types: red maculopapules, purple papules, petechiae, and raised purple scabbed areas, 3 to 10 mm. in diameter (see Fig. 1*a*, p. 259). There were red and purple maculopapules on the arms, thighs, and buttocks.

Laboratory Findings

Blood.—Haemoglobin 12·2 g. per 100 ml., white-cell count 12,700 with 81 per cent. neutrophils, eosinophil count 70-125 per c.mm., no red-cell abnormalities, platelets present in usual numbers. Corrected sedimentation rate (Rourke-Ernstene) 1·0 mm. per min. (haematocrit of 40 per cent.). Bleeding and clotting times normal. Prothrombin activity 61 per cent. Rumpel-Leede tourniquet test positive.

Urine.—Examination revealed macroscopic haematuria; sediment contained many red cells and occasional red-cell and granular casts per high-power field. Protein present in large amounts. Specific gravity 1·025.

Stools.—Guaiac reaction repeatedly positive during first 2 weeks in hospital. Some stool specimens contained flecks of red blood.

Serum albumin 3·55 g. per 100 ml.
Serum globulin 2·27 g. per 100 ml.
Serum sodium 135·9 mEq, potassium 4·5 mEq, carbon dioxide content 29·4 mEq per litre.
Non-protein nitrogen 21 mg. per 100 ml.
Cephalin flocculation test negative after 48 hours.
Bromsulphalein retention 1 per cent. after 45 minutes.
Phenolsulphonphthalein test 25 per cent. excretion of dye after 15 minutes and 75 per cent. after 2 hours.

Electrocardiogram.—Normal.

X-Ray Examination.—Chest, abdomen, and joints no abnormalities.

Clinical Course

May 11 to May 24.—During the first week in hospital her general condition was unchanged. Rectal temperatures 100° to 101° F. Tachycardia, anorexia, malaise, splenomegaly, hepatomegaly, hypertension, proteinuria, and haematuria persisted. The eyelids remained puffy but the pitting oedema of the ankles subsided. The joint pains and the slight soft tissue swelling continued, though the knee effusions decreased in size. She received 300,000 U. penicillin every 12 hours for 4 days because the throat culture revealed β-haemolytic streptococci. Biopsy (May 16) of two maculopapular lesions on the legs was consistent with the Schoenlein-Henoch syndrome.

On May 18, severe abdominal cramps recurred, the joint pains increased, and she looked much worse. New maculopapular lesions appeared on the legs, forearms, and buttocks on May 24. The liver increased in size to two fingersbreadth below the right costal margin. ACTH therapy was begun at this time and the sodium in the diet was simultaneously reduced to less than 20 mEq daily.

May 25 to May 29 (First Course of ACTH Therapy).—25 mg. ACTH were administered at 6-hourly intervals for 4 days. Symptomatic improvement commenced 1 day after the institution of therapy. She felt well, her appetite returned, the abdominal cramps ceased

completely, and the joint pains subsided. The rectal temperature was 99° to 100° F. No new skin lesions appeared and the exanthema which had developed on May 24 had become much less prominent by May 29, when a biopsy was performed. The eosinophil count fell from 81 before therapy to 31 per c.mm. 4 hours later and remained below 50 during the treatment period. The hypertension, haematuria, and proteinuria (3 to 6 g./24 hrs) persisted.

May 30 to June 5.—12 hours after the cessation of ACTH therapy, malaise, anorexia, and abdominal cramps and tenderness recurred. Marked transitory peri-orbital oedema appeared the following day. At this time the Rumpel-Leede test was negative. The eosinophil count had risen to 188. The symptoms gradually subsided only to become more severe than ever on June 4, with vomiting, and abdominal tenderness and rigidity. Fresh petechiae appeared on June 5 on the arms and legs, and the Rumpel-Leede test was found to be positive. Another skin biopsy was performed. The patient voided only 100 ml. on this day despite a fluid intake of 1,000 ml., and the blood pressure rose to 170/135. The white-cell count was 16,500 with 80 per cent. neutrophils, and there were 119 eosinophils per c.mm. It is of interest that the polymorphonuclear leukocytosis which occurred during this crisis was not accompanied by a significant fall in eosinophils such as occurs in most acute infections and surgical emergencies. It was decided to resume ACTH therapy.

June 6 to August 7 (*Second Course of ACTH Therapy*).—A total of 3,470 mg. ACTH was administered in divided doses every 6 or 12 hours as follows:

100 mg. daily for 6 days;	60 mg. daily for 4 days;
80 mg. daily for 8 days;	40 mg. daily for 7 days;
100 mg. daily for 6 days;	30 mg. daily for 12 days;
80 mg. daily for 6 days;	20 mg. daily for 13 days;

10 mg. on the last day of treatment.

The sodium intake during the period of therapy is recorded in the Table.

About 8 a.m. on June 6, a number of grand mal seizures occurred, followed by stupor and restlessness lasting 36 hours. Several minor seizures were noted later in the same day in spite of one intravenous and three subcutaneous injections of 0·1 g. sodium luminal each, and two doses of 0·2 g. dilantin. There were no abnormal neurological signs apart from a transitory extensor plantar reflex during the post-convulsive period. The optic fundi were normal. The blood pressure varied between 160/120 and 210/140. The cerebrospinal fluid was clear and the pressure was 165 mm. of water. It contained 29 red cells and two polymorphonuclear leukocytes per c.mm.

Oliguria continued through June 6. The non-protein nitrogen was 54 mg. per cent. on June 7, when the urine output rose to 750 ml. and the patient's general condition improved. On June 8 she was fully conscious, felt well, and had a normal appetite. There was no recurrence of abdominal pain. She had a retrograde amnesia for the entire period of hospitalization prior to the seizures. This gradually cleared during the next few weeks. This episode was thought to be " hypertensive encephalopathy " complicating the renal disorder. The role of ACTH in initiating the convulsions was considered non-contributory since the patient had had only 25 mg. ACTH when the encephalopathy became apparent. Moreover, the convulsions ceased and she improved rapidly despite the continuation of ACTH. The improvement in her condition was progressive and she remained free of symptoms throughout the rest of the period of ACTH therapy (Table). Her general health and appetite were excellent. The soft tissue swelling of the knees was imperceptible after 2 weeks. The spleen became impalpable on June 25 and the liver on July 4, 19 and 28 days respectively after the resumption of ACTH therapy. No new skin lesions appeared and the scabbed haemorrhagic areas present on admission slowly involuted, leaving brown, depressed scars. Skin biopsies were performed on June 13 and 19. The Rumpel-Leede test was negative on June 17 and remained negative thereafter. The blood pressure, however, continued to be persistently elevated. Haematuria varied

from gross to microscopic but was never absent. Proteinuria continued at levels between 1·9 and 16·5 g./24 hrs during this period. The specific gravity of the urine varied from 1·007 to 1·024. The non-protein nitrogen fell to 31 mg. per cent. on June 10 and remained within normal limits. There were no significant alterations in serum albumin and globulin. The phenolsulphonphthalein tests were normal (see Table). The corrected sedimentation rate varied irregularly between 0·4 and 1·3 mm. per minute, while the haematocrit and haemoglobin remained essentially unchanged. The white-cell count stayed between 11,000 and 23,000, with 75 per cent. neutrophils, during June and July, and became normal at the end of July. The eosinophil count fluctuated between 6 and 93 per c.mm. The serum sodium, potassium, and chloride values were normal, but the serum carbon dioxide content rose to 31 mEq per litre on two occasions. The electrocardiogram showed transitory flattening of T2 on June 12 and flattening of TV5 and 6 on August 2.

Marked acne of the face developed after 2 weeks of therapy. By June 25, after 3 weeks of treatment, she had gained 12 lb. in weight and there was marked pitting oedema of the feet, sacrum, and vulva, and rounding of the face. The daily dose of ACTH, which had been 100 mg., was reduced to 80 mg., and the daily sodium intake was further restricted to 8·7 mEq. The oedema subsided completely during the ensuing 3 weeks and did not recur during this treatment period.

ACTH therapy was terminated on August 7. When the patient was discharged on August 16, the only abnormalities were hypertension (varying between 140 and 160 systolic and 95 and 110 diastolic), proteinuria, haematuria, and residual skin lesions (Fig. 1*b*).

August 8 to April 8.—On August 18, while she was leading a life of moderate activity at home without dietary restrictions, she developed a mild exacerbation characterized by generalized headaches, intermittent vomiting of clear mucoid material, and painful swelling of the knees and fingers. Oedema appeared in the face and the dependent portions of the legs. The liver and spleen both became palpable two fingersbreadth below the costal margins. The blood pressure remained unchanged. She was placed on a more exacting regimen, with reduction in physical activity and sodium restriction to 20 mEq per day. A complete symptomatic remission occurred within 2 weeks, but the hypertension, proteinuria, and haematuria persisted. A skin biopsy was performed on August 24.

There were no further exacerbations in the 8 months after ACTH was discontinued. She felt well and her weight remained constant. The liver and spleen slowly receded in size. The residual pigmentation in the old skin lesions gradually faded.

The phenolsulphonphthalein excretion test and urine concentration remained within low normal limits. The endogenous creatinine clearance three months after discharge was 91 ml. per minute and after four months 99 ml. per minute corrected to 1·73 square metres of body surface (normal: 125 ± 15 ml.). The total plasma protein rose from 5·36 g. per 100 ml. to 6·3 g. per 100 ml. with a normal Albumin/Globulin ratio. The nonprotein nitrogen and serum cholesterol remained normal. The corrected sedimentation rate fell to 0·2 mm. per minute on November 30 with an haematocrit of 42 per cent. At that time the white-cell count was 9,300, the eosinophil count 86, and the Rumpel-Leede test negative (Table).

Biopsy Findings

A total of seven punch biopsies varying from 4 to 8 mm. in diameter were obtained from as many skin lesions over a period of 14 weeks.

1 *and* 2.—On May 16, 1950, 9 days before the start of hormonal therapy, and 5 to 6 weeks after the first appearance of skin involvement, two of the lesions, one " early " and one " old " (Fig. 1*a*), were removed to serve as a basis of comparison with subsequent biopsies.

FIG. 1(*a*).—May 16, 1950 (5 weeks after onset). Maculopapules, petechiae, and scabbed haemorrhagic lesions 9 days before ACTH therapy.

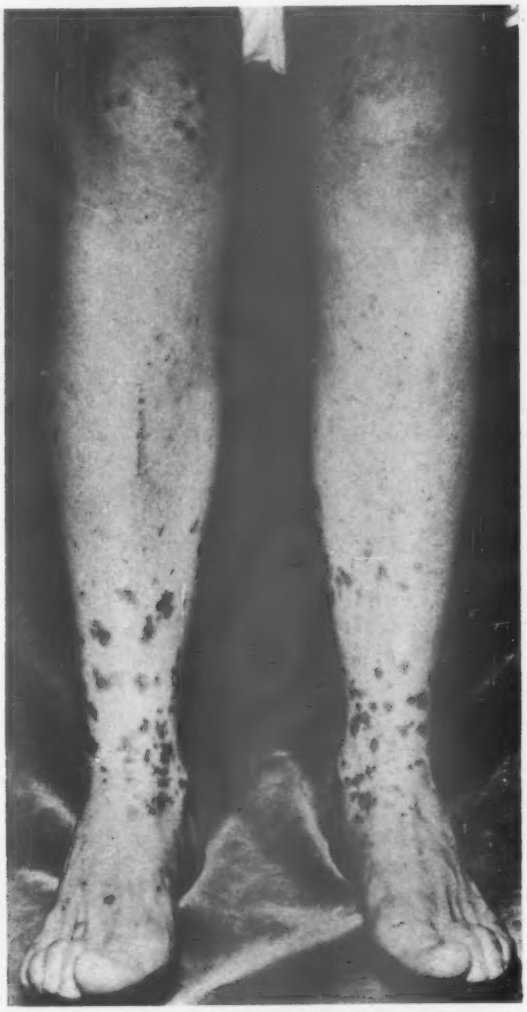


FIG. 1(*b*).—August 14, 1950 (18 weeks after onset). Depressed pigmented scars 1 week after cessation of ACTH therapy.

The "early" lesion, a red maculopapule, was examined microscopically (Figs 2*a* and *b*). A subacute inflammatory process centred in the blood vessels of the upper corium and reached its greatest intensity in the centre of the lesion. The branches of the arteriolar plexus, in particular, were outlined by heavy cellular infiltration of their walls and the perivascular connective tissue.

The infiltrate consisted of varying proportions of neutrophils, lymphocytes, and moderate-sized mononuclear cells, with large, polymorphic, vesicular nuclei and a relatively small amount of pale-staining indistinct cytoplasm. Occasional eosinophils were also present. The vascular lumens appeared to be narrowed by endothelial hypertrophy, and were occluded in several places by leukocytic and fibrin thrombi. In rare instances, there was fibrin infiltration and frank necrosis of vessel walls.

Haemorrhage was limited to the dermal papillae in the centre of the lesion, where some of the capillary loops were disrupted and surrounded by small collections of red cells. The connective tissue of the upper corium showed moderate diffuse inflammatory cell infiltration with neutrophils predominating. Occasional collagenous bundles were unusually thick and straight. The elastic fibres seemed to be fragmented. A sweat duct ran up through the centre of the lesion. The

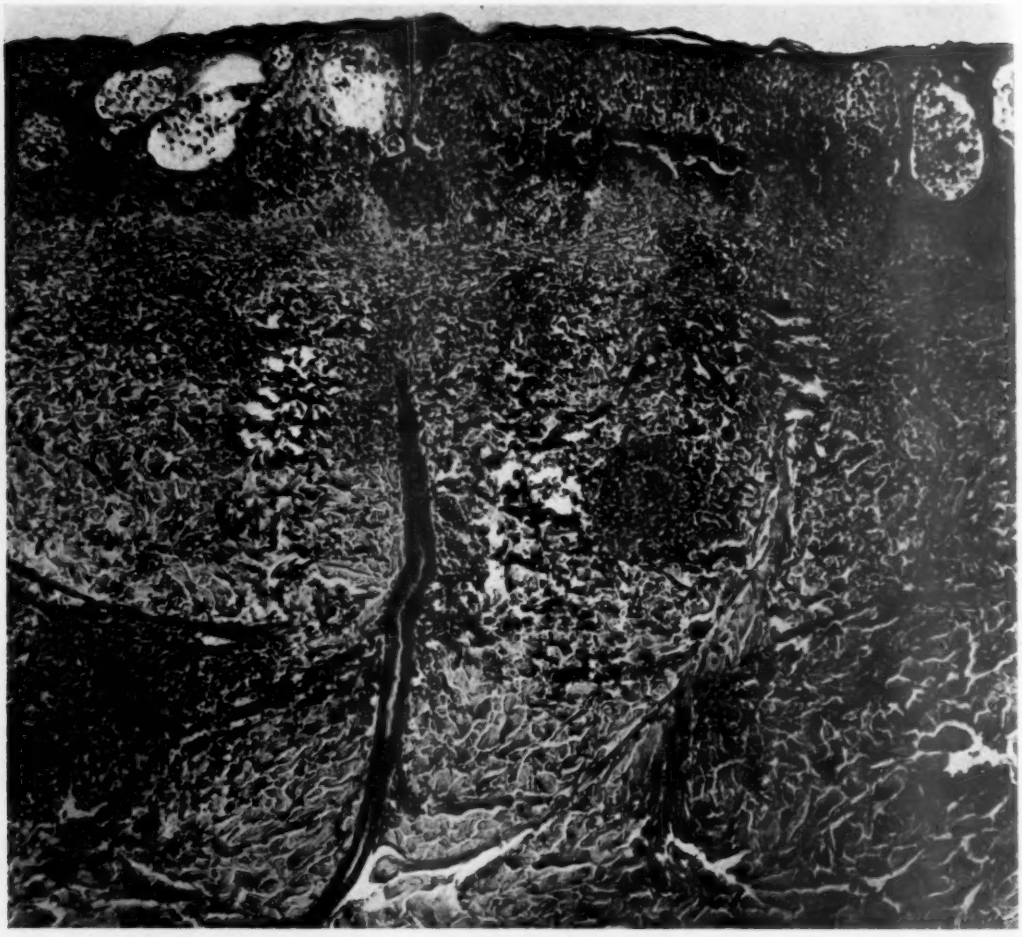


FIG. 2(*a*).—Red maculopapule before treatment. Note angiitis, central epidermal necrosis, and intra-epidermal vesicles. Haemorrhage is minimal. Haematoxylin and eosin. × 110.

epidermis was slightly acanthotic. In the central portion of the lesion there was some necrosis and neutrophil infiltration.

Intra-epidermal vesicles containing fibrino-purulent and haemorrhagic exudate were present both in the necrotic portion and the adjoining region. The lesion was consistent with those described as characteristic by Gairdner (1948).

The "old" lesion, which was grossly hard, purple, and papular, was covered by a thin crust of old purulent and haemorrhagic exudate interposed between layers of keratinized material (Fig. 3). The epidermis showed some flattening of the rete pegs. In the papillary layer of the corium there was slight proliferation of a loose, oedematous-appearing connective tissue within which there were occasional minute pericapillary extravasations and haemosiderin deposits. Rhexis of vessel walls was not seen but endothelial hypertrophy was common. The collagenous bundles in this region were unusually delicate, and elastic fibres were almost completely absent.

Inflammatory cell infiltration was limited to a minimal perivascular scattering of round cells. This lesion was evidently old both by its clinical and microscopic features. It exemplified a lesion in the course of natural evolution.

3.—The third lesion, of 5 days' duration, was removed on May 29 after 4 days of ACTH treatment. Its gross as well as microscopic appearance (Figs 4*a* and 4*b*, overleaf) was essentially similar

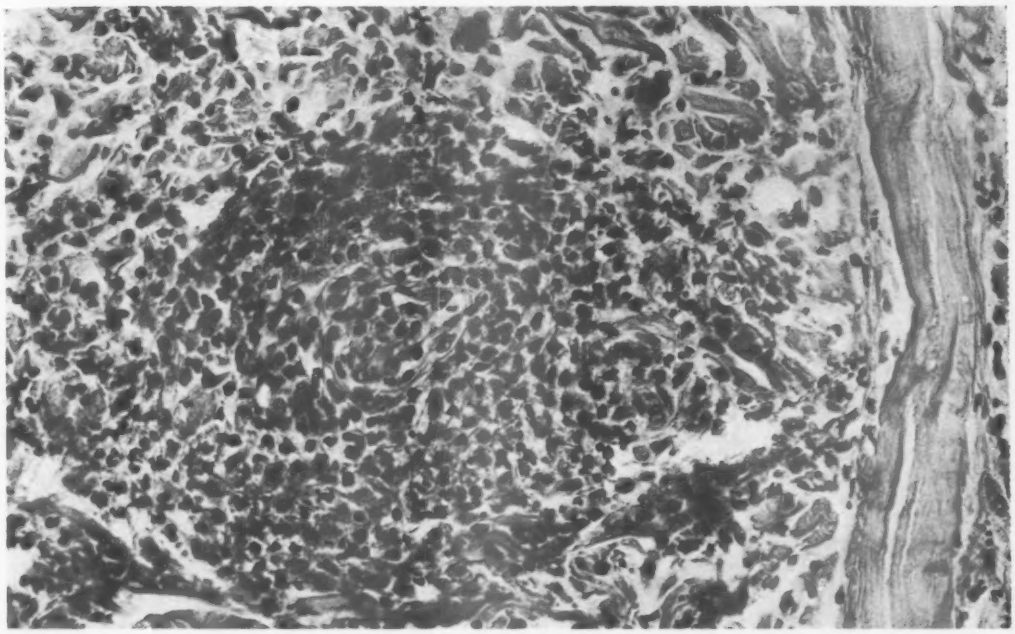


FIG. 2(*b*).—Higher magnification of vascular lesion in corium shown in Fig. 2(*a*). Note obliterative endothelial hypertrophy, intramural and perivascular infiltration of neutrophils, lymphocytes, and larger mononuclear cells, and the unusually thick and straight collagenous bundle in the adjacent connective tissue. Haematoxylin and eosin. × 400.

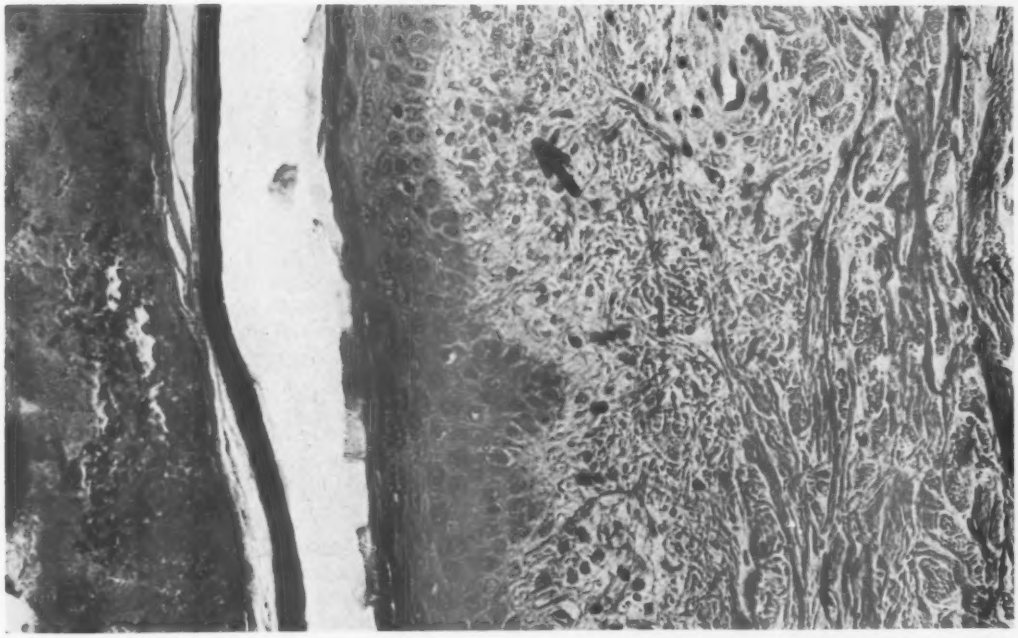


FIG. 3.—Purple papule before treatment. Note crust of old exudate, flattening of rete pegs, and oedematous-appearing papiilary layer of corium with loss of elastic fibres. The arrow points to a small extravasation of red cells in this layer. Inflammatory cell infiltration is minimal. Verhoeff's elastic-tissue stain and Van Gieson. × 340.

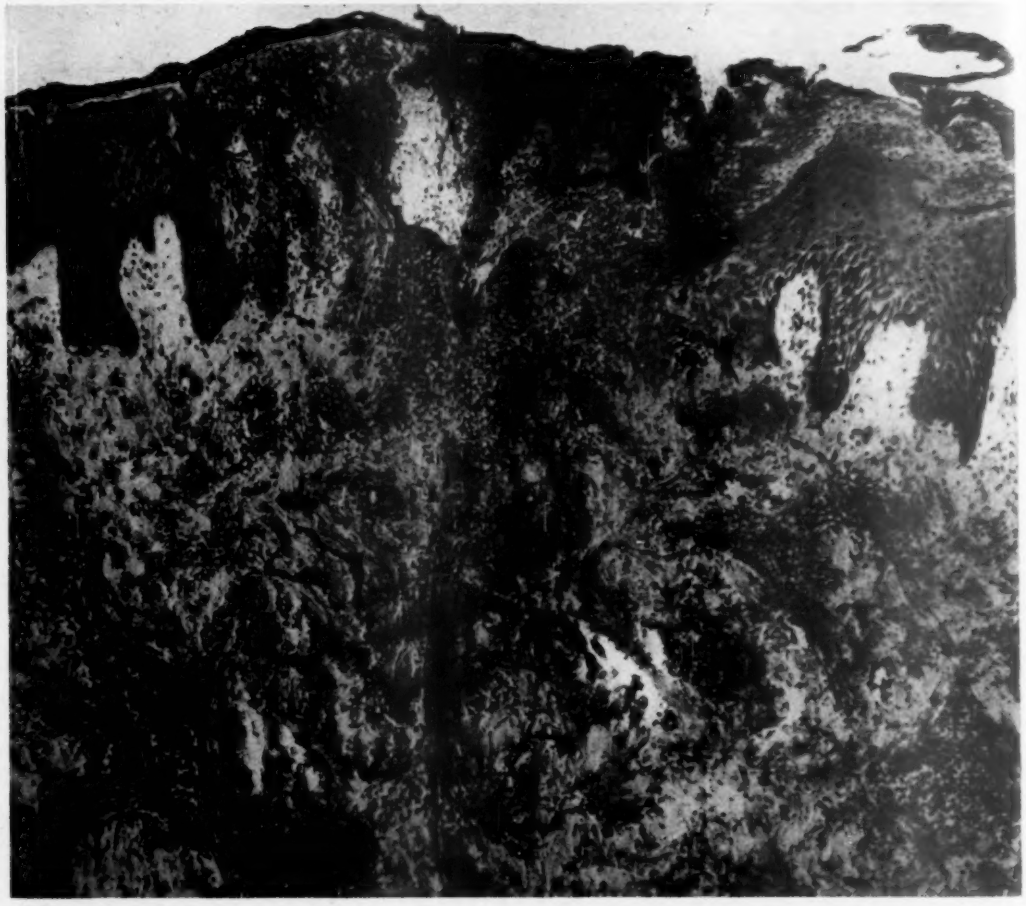


FIG. 4(*a*).—Red maculopapule of 5 days' duration after 4 days of ACTH therapy. In the lower left-hand corner an arteriole and its branches are outlined by inflammatory cell infiltration. Haematoxylin and eosin. × 110.

to that of the "early" red maculopapule removed before treatment. There was an intense, subacute angiitis of the upper corium with heavy mononuclear and polymorphonuclear cell infiltration, focal thrombosis and occasional necrosis with fibrin infiltration of vessel walls. Several central subepidermal capillary loops were disrupted and surrounded by small extravasations of red cells. The overlying epidermis showed vesicle formation, necrosis, and neutrophil infiltration. There was also considerable diffuse neutrophil infiltration in the upper corium, particularly about the arrectores pili. A sweat duct ran up through the centre of the lesion. The collagenous framework was slightly coarser and more compact, and stained more heavily with eosin or aniline blue in the centre of the lesion than in the adjacent regions. There was nothing to suggest that the four-day course of ACTH had exerted any ameliorating effect.

4.—The fourth lesion was removed on June 5, 7 days after cessation of the first course of therapy and 1 day after the onset of an exacerbation of the disease with abdominal pain and appearance of new petechiae. The lesion was of the "old", papular type representing a healing haemorrhagic bulla. Microscopically, it showed a rather diffuse scattering of well-preserved extravasated red cells in the superficial layer of the corium. This layer was thickened, and consisted of newly-formed, loose, pale-staining connective tissue with delicate collagenous bundles, absence of elastic fibres, a slightly haematoxylinophilic ground substance, and plump fibroblasts. The cells of the blood-vessel walls were hypertrophied and the lumens were narrowed by the

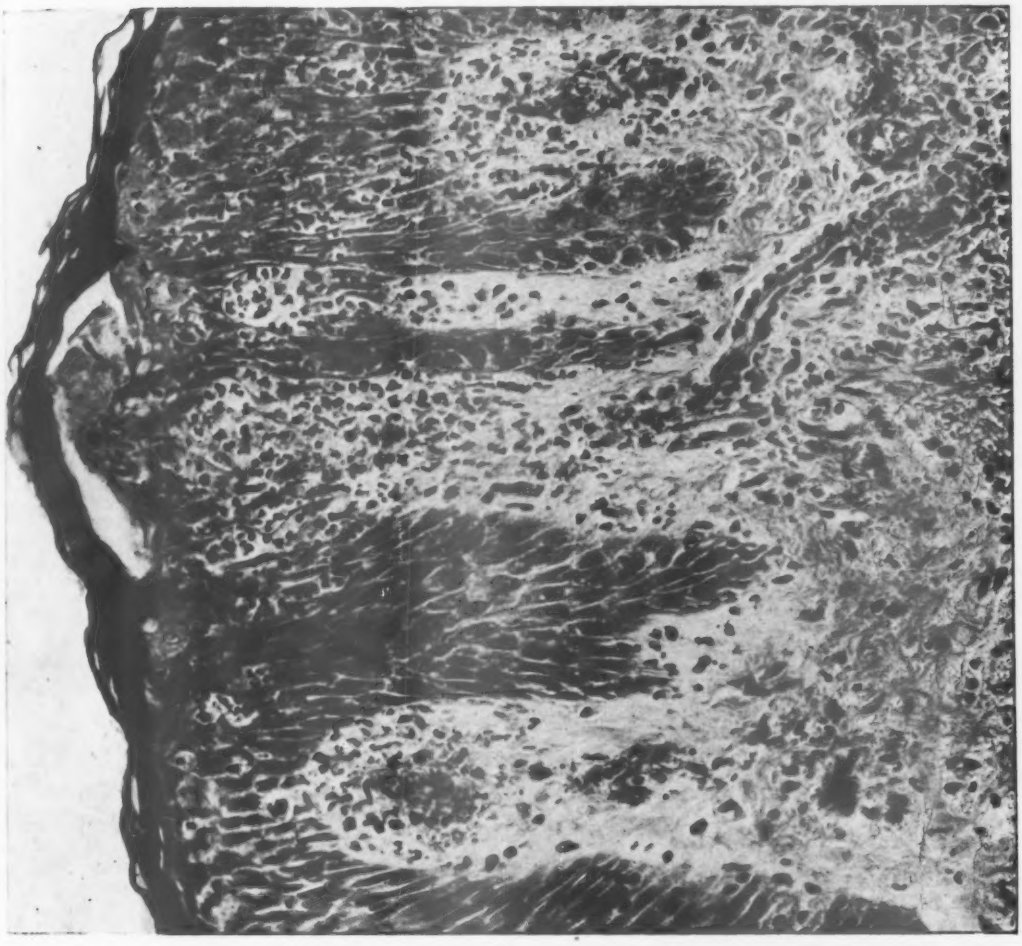


FIG. 4(*b*).—Higher magnification of intra-epidermal vesicle in another section from the same lesion as Fig. 4(*a*). There is focal thrombosis and disruption of capillary loops with some extravasation of red cells. The epidermis shows focal necrosis, neutrophil infiltration, and acanthosis. Haematoxylin and eosin. × 340.

inward bulging endothelium. There was no increased vascularity or disruption of vessels. There was minimal lymphocytic infiltration and slight perivascular haemosiderin deposition, mostly in the deeper portions of the corium. The epidermis over the central part of the lesion was somewhat atrophic, with absence of the rete pegs, and was separated slightly from the underlying corium, leaving a small fluid-filled cleft. The general features of this lesion were essentially similar to those of the purple papule examined before the start of therapy, but the amount of haemorrhagic extravasation and fibrous proliferation in the corium were more extensive. The extravasation appeared to be the result of the escape of red cells through the intact vessel walls, and was thus quite different from the inflammatory rhexis of capillaries in the acute lesions. The possibility that operative trauma was a causative factor could not be excluded. The localization of the extravasation to the region of proliferating connective tissue may have been related to the absence of supporting perivascular elastic fibres (Peck and others, 1937), to the immature character of the endothelium, or to a change in the ground substance.

5.—The fifth skin biopsy was performed on June 13, 1950, 7 days after the start of the second course of ACTH, and 8 days after the last exacerbation of the disease. The lesions were all somewhat flatter and browner than those previously described. The histological findings differed

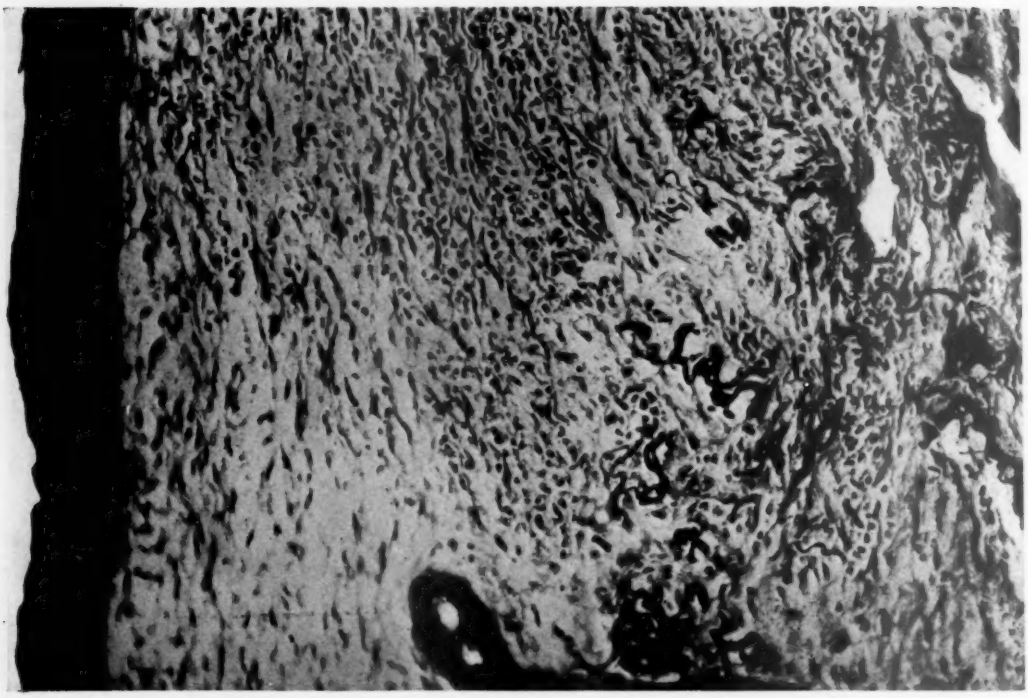


FIG. 5.—Depressed brown scar after 13 days of ACTH therapy. The epidermis is atrophic. The superficial corium is devoid of elastic fibres, appears oedematous, and contains diffusely scattered red cells. Verhoeff's elastic-tissue stain and Van Gieson. × 340.

little from those of the fourth biopsy. Fibrosis of the corium, haemosiderin deposition, and atrophy of the epidermis, were slightly more advanced. Haemorrhagic extravasations were more discreet but measured up to 0·5 mm. in diameter. One small subpapillary vessel contained a necrotic thrombus.

6.—The sixth biopsy was performed on June 19, after 13 days of ACTH therapy. The lesions had become depressed brown scars. Microscopically (Fig. 5) the features resembled those of the fifth biopsy. Fresh-appearing extravasated red blood cells were again diffusely scattered through the newly-formed connective tissue of the upper corium.

7.—At the time of the seventh biopsy on August 24, 17 days after the cessation of the 2-month course of ACTH, and 3 months after the last crop of skin lesions had appeared, brown scars persisted but were somewhat less depressed (Fig. 1*b*). On histological examination, the epidermis, which had been atrophic, appeared almost normal with re-formed rete pegs. Haemorrhages had disappeared, and the upper corium showed a normal pattern of elastic fibres. However, slight perivascular infiltration of lymphocytes and plasma cells, as well as scattered haemosiderin granules, remained.

In summary, the 5-day-old maculopapular lesion removed at the end of the first 4-day course of ACTH treatment did not differ significantly from the " early " lesion removed before the start of treatment. Both were characterized by an intense subacute angiitis of the upper corium with mononuclear as well as polymorphonuclear leukocytic infiltration, some capillary rhexis, and segmental vascular necrosis, slight perivascular extravasation of red cells, and necrosis and vesicle formation in the overlying epidermis. A biopsy of a papular lesion, taken 7 days after cessation of the first course of therapy at a time when new purpuric lesions were appearing, and biopsies of comparable lesions, taken respectively on the seventh and thirteenth days of the second course of ACTH, were all essentially similar on microscopic examination. They resembled the involuting

pretreatment lesion in showing only minimal inflammatory cell infiltration. Fibrosis, epidermal atrophy, haemosiderin deposition, and extravasation of fresh-appearing red cells were more extensive in all three of these lesions than in either of the pretreatment "controls", despite the absence of capillary rhexis. The seventh biopsy, taken 17 days after cessation of the 2-months' course of ACTH, showed almost complete reversal of all microscopic changes, except for slight perivascular round-cell infiltration.

Discussion

The nosological status of the Schoenlein-Henoch syndrome is difficult to evaluate. Some (Gairdner, 1948) believe it to be a "clear entity"; others (Osler, 1914; Davis, 1948) suggest that a variety of aetiologic factors, which may or may not be related, evoke a similar host response and result in a similar clinical picture. It is known that the triad of non-thrombopenic purpura, articular symptoms, and gastro-intestinal symptoms can occur in disseminated lupus erythematosus, polyarteritis nodosa, rheumatic fever, and serum sickness, and that nephritis may be a manifestation of these diseases. Unfortunately, no systematic comparative study has yet been made of the purpuric lesions in these diseases, purpura simplex, and the Schoenlein-Henoch syndrome. Nevertheless, Gairdner (1948) believes that the exanthema of the Schoenlein-Henoch syndrome is sufficiently characteristic to be recognizable both clinically and histologically. He points out that recurrent crops of red maculopapules, with or without purpura, are found in variable combination with gastro-intestinal symptoms, articular symptoms, and nephritis, all of which, as he believes, probably result from a vascular lesion. He stresses that an acute aseptic inflammatory reaction around the vessels of the upper corium, frequently associated with a tissue eosinophilia, forms the basis of the exanthema. Our case fulfils both the clinical and the histological criteria of Gairdner's definition.

The clinical course of the syndrome is variable. There may be only one attack or there may be attacks recurring for periods of a few months up to 50 years (Osler, 1914; Davis, 1948). Individual skin lesions may disappear within a few hours, days, or weeks, but may persist as pigmented scars for many months. Gairdner (1948) states that the maculopapules typically disappear within 2 weeks. The gastro-intestinal and articular symptoms are also variable in both duration and severity. The inconstant incidence and course of the renal lesions in illustrated by the fact that eleven of Gairdner's twelve cases had renal involvement, of whom one died in renal failure and four went on to chronic or latent nephritis, whereas only four of the 44 cases of Davis (1948) showed renal disease, and only one of these had albuminuria at the end of 3 months.

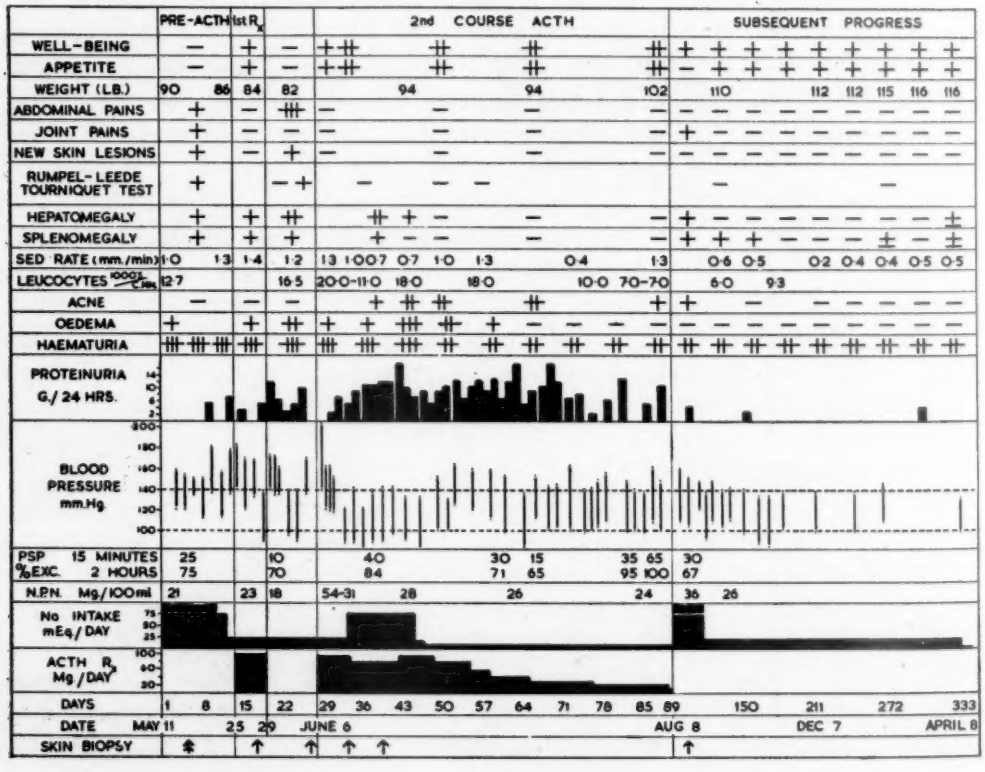
The difficulty of assessing any therapeutic procedure in a disease so subject to spontaneous exacerbations and remissions as the Schoenlein-Henoch syndrome is self-evident. None of the modes of therapy other than ACTH, which have been tried in this condition, has been shown to exert a consistently favourable influence. The use of ACTH for a 2-week period in one case has been reported by Stefanini and others (1950), who found that the abdominal pain, which had been present intermittently in the 24 days before therapy, subsided "early" during therapy and that the petechial rash, which appeared 6 days before ACTH was administered, did not

disappear until after 6 days of treatment. Small numbers of new petechiae appeared in the skin even during this period. Urinary findings showed a slight though transient improvement. The biopsy of an area of fresh haemorrhage taken at the start of therapy showed mainly active inflammation centred about the small vessels of the corium. The biopsy of a similar area of fresh haemorrhage taken at the cessation of therapy showed massive haemorrhage but only minimal perivascular lymphocytic infiltration. Purpuric spots and abdominal symptoms recurred briefly 6 days after the suspension of treatment. An exacerbation of skin and renal symptoms occurred one month later.

Our own results (see Table) are similar in many ways to those of previous authors. The institution of the first course of ACTH was followed within 24 hours by striking improvement in the constitutional, abdominal, and joint manifestations, but the constitutional and abdominal symptoms recurred 12 hours after the drug was sustained, improvement within 2 days. A mild temporary return of constitutional, abdominal, and joint manifestations was noted on the eleventh day after the cessation of the second course of therapy. In spite of the prompt improvement of all other features, hypertension, haematuria, and proteinuria persisted throughout the two courses of treatment and were still present 12 months after the onset

TABLE

CONSTITUTIONAL, ABDOMINAL, ARTICULAR, EPIDERMAL, RENAL, AND VASCULAR MANIFESTATIONS



of the illness. It is still too early to say whether the nephritis will progress in this case, but there is no evidence that the course of the renal disease was significantly affected. This is in agreement with the results of ACTH therapy in other forms of Bright's disease (Farnsworth, 1950; Brunsting and others, 1950; Thorn and others, 1950; Burnett and others, 1950; Shick and others, 1950).

The effect on the cutaneous lesions is difficult to interpret because of the variability in their clinical appearance and course. In favour of a salutary effect are the failure of new lesions to develop during therapy, and the fact that fresh petechiae appeared when the first course of ACTH was stopped. Moreover, inflammatory exudation was minimal in the biopsies taken after more than 4 days of treatment. On the other hand, an untreated " old " lesion, which grossly resembled those removed during therapy, showed equally slight inflammation, and a 4-day course of ACTH failed to alter appreciably the evolution of a lesion which appeared the day before therapy was initiated. The mechanism of fresh haemorrhage in " old " lesions as long as 13 days after the beginning of ACTH therapy is obscure, and the possibility cannot be excluded that operative trauma played a role.

Thus, it seems possible that ACTH may inhibit the development of new inflammatory skin lesions, but it is not established that the regression of existing lesions can be significantly altered.

It should be emphasized that further studies are needed before an adequate evaluation of ACTH in the treatment of the Schoenlein-Henoch syndrome is possible. It would seem important to undertake therapy early in the course of the disease. The study of biopsy material would have greater value if the microscopic evolution of the untreated skin lesions were more exactly known, and if lesions removed before and during treatment were matched whenever possible before therapy as regards date of appearance and clinical characteristics.

Summary

(1) A case is presented with the classical features of the Schoenlein-Henoch syndrome, including nephritis.

(2) Each of two courses of ACTH therapy was followed by prompt and progressive improvement in the constitutional, abdominal, and joint manifestations. Exacerbations occurred after withdrawal of the drug in both instances.

(3) No skin lesions appeared during therapy, but there was a new crop of petechiae in the interval between the two courses of ACTH. Histological study failed to establish that the regression of existing skin lesions was significantly hastened.

(4) The evidence of renal involvement (hypertension, proteinuria, and haematuria) persisted in spite of 9 weeks of ACTH therapy, and was still present 12 months after the onset of the illness.

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Action de l'ACTH dans le Syndrome de Schoenlein-Henoch: Rapport sur un Cas, avec Étude Histologique des Prélèvements de la Peau

RÉSUMÉ

(1) On décrit un cas présentant des traits classiques de syndrome de Schoenlein-Henoch, y compris la néphrite.

(2) Chacune des deux séries de traitement à l'ACTH fut suivie d'une amélioration prompte et progressive des manifestations générales, abdominales, et articulaires. Il y eut des exacerbations chaque fois qu'on arrêtait le traitement.

(3) Pendant le traitement les lésions cutanées n'apparurent pas, mais il y eut une poussée pétéchiale pendant l'intervalle entre les deux séries de l'ACTH. L'étude histologique n'a pas réussi à établir que la disparition des lésions cutanées existantes ait été accélérée d'une manière significative.

(4) Les signes de l'atteinte rénale (hypertension, albuminurie, et hématurie) persistèrent malgré neuf semaines de traitement par l'ACTH et étaient encore présents douze mois après le début de la maladie.

Acción de la ACTH en el Sindrome de Schoelein-Henoch: Informe sobre un Caso, cíon Biopsias de la Piel

SUMARIO

(1) Se presenta un caso con las clásicas características del síndrome de Schoenlein-Henoch, incluyendo nefritis.

(2) Cada uno de dos tratamientos por la ACTH fué seguido por mejoría rapidá y progresiva de las manifestaciones generales, abdominales, y articulares. Exacerbaciones ocurríeron cada vez que se interrumpió el tratamiento.

(3) Durante el tratamiento no aparecieron lesiones cutáneas, pero hubo un brote petequial en el intérvalo entre las dos series de ACTH. Los estudios histológicos no lograron establecer que la desaparición de las lesiones cutáneas presentes fuese acelerada de manera significativa.

(4) Evidencia de complicación renal (hipertensión, albuminuria, y hematuria) persistió a pesar de que el tratamiento por ACTH se extendiese por nueve semanas y se la pudo constatar aún después de doce meses contados desde el principio de la enfermedad.

DIFFERENTIAL TISSUE AND ORGAN ANOXIA IN DISEASE: THE MEASUREMENT OF PERI-ARTICULAR OXYGEN SATURATION LEVELS IN PATIENTS WITH ARTHRITIS*

BY

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Introduction

A number of investigations testify to the association of vascular factors with joint disturbances. The Scientific Advisory Committee of the Empire Rheumatism Council concluded, as a result of a carefully controlled investigation (1950), that peripheral vascular abnormalities are not only associated with rheumatoid arthritis but frequently ante-date its onset; Davis (1941) analysed 88 cases in 27 families in which spontaneous ecchymoses had occurred, and concluded that an intimate relationship exists between arthritis and purpuric manifestations; Fletcher (1947) states that patients with rheumatoid arthritis usually have cold, clammy hands, the skin of which assumes the temperature of its surroundings sooner than the skin of normal persons, while the reaction to heat and cold is poor and slow. Increased periarticular vascularity, perivascular lymphocytic infiltration of the synovial membrane, and periarticular rheumatic arteritis resembling periarteritis nodosa, are described as typical of the pathology of rheumatoid arthritis. Factors connected with the functions of the capillaries have been investigated in cases of arthritis and abnormalities described: thus Race (1937) found a low blood ascorbic acid level in patients with all types of rheumatism, and Fletcher (1947), commenting on Race's work, remarks:

> although it is fairly clear that lack of vitamin C is not the cause of rheumatoid arthritis, it may well be one of the factors concerned in its production.

Vitamin K has been similarly implicated, Rawls and others (1935) having described a low prothrombrin level in half their series of patients with rheumatoid arthritis. As with function, so with structure: capillary spasm, slowed blood flow, and distortions of the normal morphological capillary patterns, have all been described (Fox and Van Breemen, 1934). Finally, the local treatment of rheumatic disorders by means of oil of wintergreen and other rubefacients, injection of thiohistamine, massage, ultra-violet light, and various types of heat application from infra-red to hot wax baths, is treatment acting primarily on the vascular components of the disease process and achieves a success which is often in direct relationship with its efficacy in this respect.

* This work was done during the tenure of a Nuffield Foundation travelling Fellowship in Medicine.

The present study attempts the investigation of a further variable of the vascular complex comprising the local components of the arthritic process, i.e. that concerned with the periarticular oxygen metabolism.

Experimental Methods and Clinical Material

Two oximetric techniques were used concurrently. The Millikan photo-electric oximeter (Millikan, 1942) was used to determine the arterial blood oxygen saturation levels of the general circulation (recording from the minute vessels of the pinna of the ear) after preliminary flooding of the circulation with 100 per cent. oxygen by inhalation through a mask to standardize the instrument. With such equipment Millikan obtained agreement to within ± 5 per cent. in the upper range against *in vitro* Van Slyke manometric determinations made on blood withdrawn from human subjects by arterial puncture.

For the periarticular determinations, a modification (Lovett Doust, 1951) of the " Reduction Time " method described by Ray (1946) was used. In contrast with the continuous oximetric analysis carried out by the Millikan instrument, the reduction time or spectroscopic oximetry technique is discontinuous and dependent upon the fact that the absorption bands of oxyhaemoglobin, when observed from heated, illuminated, histaminized skin through a pocket spectroscope, disappear after occlusion of the peripheral circulation at a rate proportional to the degree of saturation of the haemoglobin with oxygen. It was found to be possible to train the spectroscope on any reasonably thin area of skin of the hands or wrists and to get highly reliable results. Using the skin of the dorsum of the hand in a large number of healthy subjects, Ray (1946) found a correlation coefficient of $+0{\cdot}87$ between the reduction time and the alveolar oxygen tension.

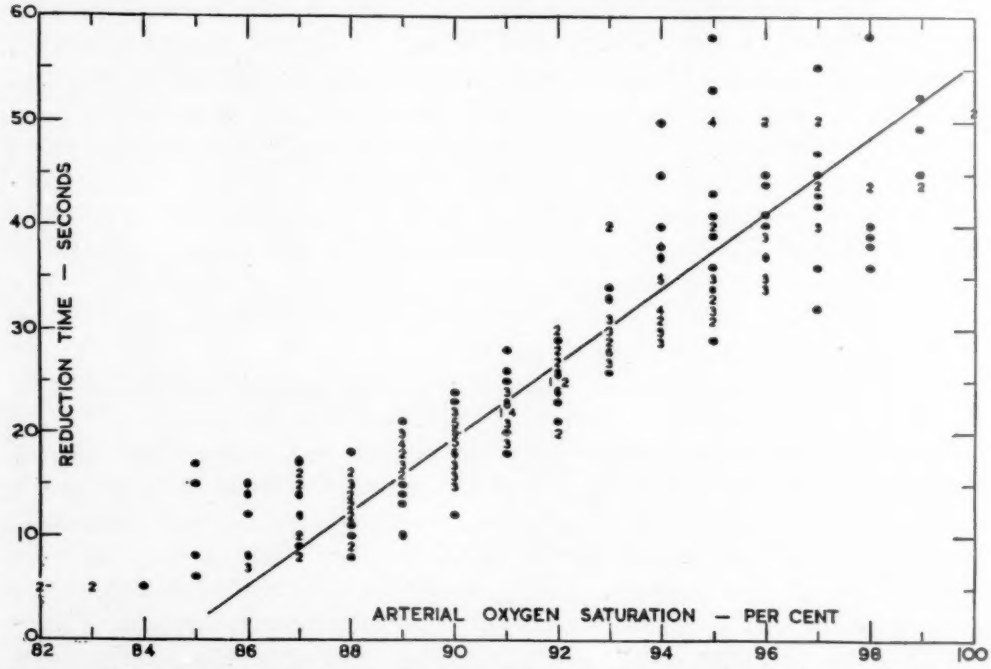

FIG. 1.—Calibration graph of 285 simultaneous oximetric determinations made on healthy, non-arthritic subjects.

Ordinates are results obtained by spectroscopic reduction-time method on skin vessels of finger, expressed in seconds. Abscissae are results obtained by the photo-electric oximeter on vessels of pinna of ear in percentage arterial oxygen saturation. Line of regression obtained from a regression equation yielded a correlation coefficient of $+ 0{\cdot}92$.

Cross correlation of the two methods of oximetry, in a series of 285 simultaneous observations by the present writer (Fig. 1), shows a satisfactory degree of agreement between them ($r = +0{\cdot}92$).

In the present investigation, periarticular oximetry was carried out by focussing the spectroscope on the skin around the various joints of the fingers and hands.

Control Group.—The joints chosen were the proximal interphalangeal joint of the left ring finger (L.4 p.i.p.) and the distal interphalangeal joint of the left index finger (L.2 d.i.p.). This was an arbitrary and convenient choice of location. The results in this group for all periarticular regions of the fingers were similar for any one individual and at any one time wherever the measurements were taken, always providing no local skin lesions were present and no pathology was involving the joint under investigation.

The controls were a group of 35 apparently normal healthy subjects of both sexes whose ages ranged from 18 to 46 years. They were investigated in exactly the same way as the patients with arthritis.

Patients.—This was an unselected group, the only criterion for inclusion being an unequivocal diagnosis of some form of arthritis affecting the joints of the fingers. Most patients suffered from the rheumatoid type of atrophic arthritis but few were uncomplicated by other conditions (Table I). There were eight females and two males in the series and their ages ranged from 15 to 62 years. They all had objective clinical evidence of their disability, varying from slight degrees of swelling, pain, and limitation of movement in one or more joints up to gross deformities affecting practically all joints of both hands

TABLE I

BASIC DATA ON TEN CASES OF ARTHRITIS AND 35 HEALTHY CONTROLS

Case No.	Sex	Age (years)	Arterial Blood Oxygen Saturation per cent.—Range			Local Clinical Activity (4-point scale)	Principal Diagnosis	Ancillary Diagnoses
			General blood stream (ear)	Joints				
				Unaffected	Affected			
1	M	19	93-95	91-94	86-92	+	*R.A.	Postural scoliosis Emotional immaturity
2	F	18	92-96	92-96	88-90	++	R.A.	Muscle tension syndrome
3	F	39	96-97	96-97	85-86	++++	R.A.	Osteo-arthritis Tinnitus Dyspepsia
4	F	36	95-96	94-95	90-91	++	R.A.	—
5	M	28	96-97	96-97	92-93	+	R.A.	Cervical osteo-arthritis Migraine
6	F	15	92-94	92-94	85-87	++++	Arthritis mutilans	Old Still's disease Cervical dislocation
7	F	62	91-94	91-94	89-92	++	R.A.	Osteo-arthritis Essential hypertension
8	F	29	97-98	97-98	92-93	+++	R.A.	Psoriasis
9	F	19	96-97	96-97	88-90	+++	R.A.	Pruritus Skeletal muscle tension syndrome
10	F	44	95-97	95-97	91-93	++	R.A.	Obstipation Corneal opacities Depression
35 Controls	15 F 20 M	18-46	93-98	93-98	—	—	—	—

* R.A. = Rheumatoid type of atrophic arthritis.

and many others elsewhere in the body. The youngest member of the group suffered from the sequelae of Still's disease contracted 3 years previously and *arthritis mutilans* was present to a very considerable degree: the patient could not walk and could stand, with support, only for periods up to 4 minutes at a time.

The spectroscopic and photo-electric techniques of oximetric examination were employed simultaneously, all measurements being checked until concordance was obtained, in the case of spectroscopic method, to within a difference of one second between the results in any one individual.

Results

These are shown in detail in Tables I to III and in Fig. 2.

Spectroscopic Oximetric Assay in Superficial Inflammation.—One member of the control group accidentally contracted a small acid burn on the finger-nail fold of the right middle finger during his work as a laboratory assistant. A small indolent abscess resulted, and an area a few millimetres in diameter was slightly warm to the touch, and red in colour with a tinge of blueness towards the periphery.

TABLE II

COMPARISON OF LOCAL CLINICAL STATE AND DEGREE OF PERIARTICULAR ANOXIC INVOLVEMENT

Complete survey of finger joints of both hands in Case 6.
One finger (L. middle) was apparently completely spared: all the rest were severely affected.

Joint Examined	Right Hand			Left Hand		
	Reduction Time (secs.)	Equiv. O_2 Saturation (per cent.)	Clinical Status	Reduction Time (secs.)	Equiv. O_2 Saturation (per cent.)	Clinical Status
1 m.p.	23	91·5	SW.D.	14	88·5	D.P. & T.
1 i.p.	23	91·5	SW.D.	17	89·4	D.P. & T.
2 m.p.	21	91·0	SW.D.	20	90·5	SW.D.
2 p.i.p.	23	91·5	SW.D.	20	90·5	SW.D.
2 d.i.p.	19	90·0	SW.D.P. & T.	23	91·5	D.
3 m.p.	29	93·5	Normal	20	90·5	D.
3 p.i.p.	29	93·5	Normal	24	91·8	D.
3 d.i.p.	27	92·8	Normal	23	91·5	D.
4 m.p.	23	91·5	SW.D.	14	88·5	D.P. & T.
4 p.i.p.	23	91·5	SW.D.	18	89·7	D.P. & T.
4 d.i.p.	21	91·0	SW.D.	21	91·0	D.P. & T.
5 m.p.	15	88·8	SW.D.P. & T.	14	88·5	D.P. & T.
5 p.i.p.	15	88·8	D.P. & T.	11	87·5	D.P. & T.
5 d.i.p.	15	88·8	D.P. & T.	10	87·2	D.P. & T.

Topographic shorthand follows that of Fletcher (1947).

TABLE III

RESULTS OF LOCAL TISSUE OXIMETRY ON A SMALL ACID BURN OF FINGER-NAIL FOLD IN NORMAL SUBJECT

Effect of healing and correlation of oximetric analysis and clinical appearances.

Date	Oxygen Saturation per cent. General Circulation (photo-electric determination)	Local Tissue Oximetry of Lesion (spectroscopic method)		Remarks
		Equivalent O_2 per cent.	Reduction Time (sec.)	
6.6.50	94-96	89·5	17	Indolent area of superficial inflammation. Calor et rubor
19.6.50	94-96	91·4	23	Healing satisfactorily
22.6.50	94-96	90·0	19	Reinfected by scratching
29.6.50	94-96	93·0	28	Healing
19.7.50	94-96	96·0	40	Healed

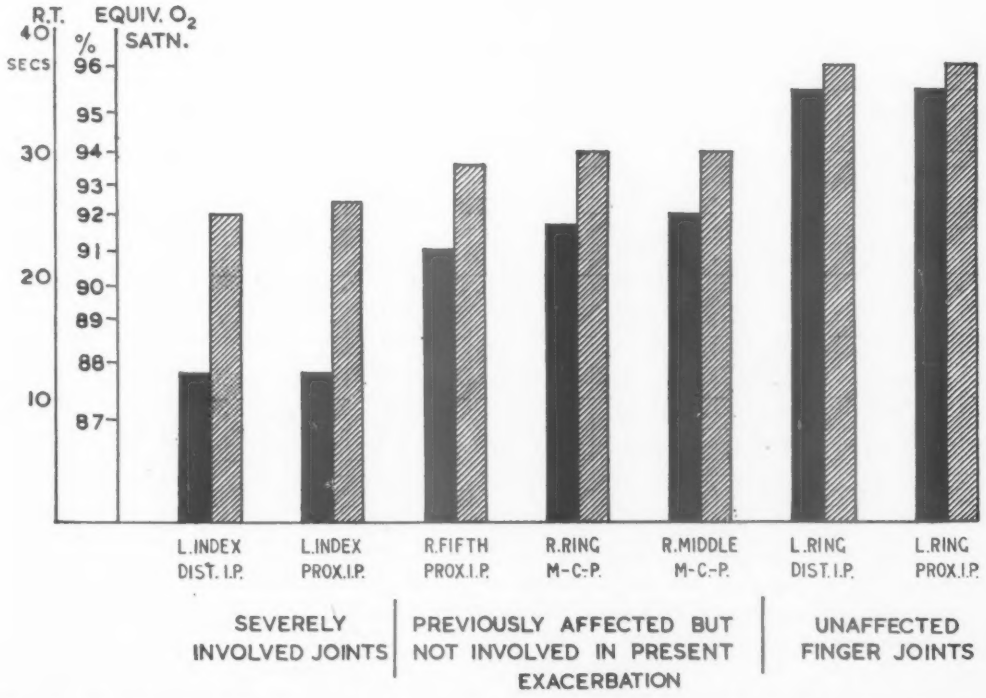

FIG. 2.—Female, aged 39 (Case 3). Results of a periarticular, spectroscopic, oximetric assay on three groups of joints (blackened histogram) compared with results of a repeated assay after inhalation by patient of 100 per cent. oxygen through a mask (hatched areas). Note periarticular anoxia of severely affected joints and concordance of clinical state with oximetric results.

Clinically it represented a very small disability and the subject had no thought of seeking treatment for it, discussing it as something which would heal unaided. Oximetrically, despite the turgor and apparent adequacy of blood supply, the lesion proved to be anoxic, although the blood of the skin vessels immediately beyond it showed a normal concordance with the arterial oxygen saturation levels of the general blood stream. Table III details these data and shows the changes taking place in longitudinal section as the lesion healed over a period of weeks.

Periarticular Oximetric Survey of Arthritic Finger Joints.—Complete surveys were made of all affected and unaffected finger joints in the ten cases of arthritis investigated. Such an individual assay occupied about 45 minutes for any one subject and required very little co-operation from the patient. The data obtained from the group are contained in Table I, which includes the mean results given by the control group for comparison. The individual results of an oximetric survey in a very severely disabled girl, in whom only one finger had been spared from a widespread and still active rheumatoid arthritis, are listed in Table II. A general correspondence between the level of local periarticular anoxia and the clinical intensity of the arthritic process was noted. Fig. 2 gives the partial results in histogram form of a similar survey in another case of rheumatoid arthritis.

Influence of Oxygen Inhalation.—Fig. 2 also shows the effects of inhaling 100 per cent. oxygen, through a B.L.B. type mask, on the periarticular oxygen saturation levels of anoxic arthritic joints. It will be observed that even grossly affected joints are capable of considerable oxaemic response, even up to levels within the critical range for normality.

Discussion

Objective methods of assessing the extent, degree, and capacity for change, of joint involvement in patients with arthritis have been lacking in the past, but recently a number of techniques have been introduced to this end. The four clinical tests of Quin and others (1950) have been criticized by Harris (1950) as unreliable, misleading, and not even objective, and the system devised by Steinbrocker and others (1949) can only handle gross changes taking place over a period of months. On the other hand, skin thermometry (Hartfall and Harris, 1949), and the technique of measuring blood flow described by Kellgren and Janus (1950), which depend upon all-important peripheral vascular factors, are not only quantitative but also completely objective. It would seem probable that the last two methods are influenced by the same variables as the method of oximetric assay reported here and the somewhat similar methodology suggested by Jarløv and Jarløv (1950).

It is also interesting to recall that the exhibition of oxygen has long been considered to be indicated in a number of different rheumatic disorders. Oxygen inhalation, breathing exercises, and the cautious transfusion of whole blood, are sometimes advised in the management and treatment of rheumatoid arthritis, while

for cases of sciatica and fibrositis, even the local subcutaneous *injection* of oxygen is stated to have proved successful in intractable cases (Copeman, 1947).

The spectroscopic oximetry technique described here would appear to provide a rapid and convenient method of objective assessment of the degree of involvement of arthritic joints. The results of such an oximetric assay could be used also to evaluate the prognostic implications involved in the differential reversal of the local anoxia by oxygen inhalation.

Summary

(1) Two methods of oximetry were employed concurrently to estimate the arterial blood oxygen saturation levels of the general circulation (photo-electric technique) and of the periarticular skin vessels (spectroscopic technique) around arthritic joints. Subjects included 35 healthy controls and ten patients with the rheumatoid form of atrophic arthritis.

(2) It was found that in patients with arthritis, though not in healthy controls, a dissociation between the oxygen saturation levels recorded by the two oximetric methods had occurred, the periarticular vessels showing a degree of anoxia which bore a relationship to the apparent degree of local clinical arthritic involvement. No generalized anoxaemia was found on routine examination in either patients or controls.

(3) It was found possible oximetrically and quantitatively to assay both superficial peripheral cutaneous lesions and the periarticular tissues of suspected arthritic joints for the presence of local anoxia. The advantages of such an objective method of assay in rheumatoid arthritis are discussed.

(4) It is shown that the anoxia around affected joints is temporarily reversible after the administration of oxygen by inhalation.

I am indebted for facilities enabling this investigation to be carried out, to Professors Harold G. Wolff and Stewart Wolf, of the Department of Medicine, Cornell University Medical College, New York Hospital, and to Professor Aubrey Lewis, of the Institute of Psychiatry, Maudsley Hospital, London.

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Anoxie Différentielle des Tissus et des Organes au Cours de la Maladie: Mesure Périarticulaire des Points de Saturation par l'Oxygène chez les Malades Atteints d'Arthrite

Résumé

(1) On s'est servi concurremment de deux méthodes oxymétriques pour déterminer les points de saturation par l'oxygène du sang artériel de la circulation générale (procédé photo-électrique) et du sang des vaisseaux de la peau (procédé spectroscopique) autour des articulations arthritiques. Trente-cinq témoins sains et dix malades atteints d'arthrite atrophique à forme rhumatismale furent soumis à cette étude.

(2) On a trouvé chez les arthritiques—mais pas chez les témoins—qu'il y avait une dissociation entre les points de saturation par l'oxygène déterminés par les deux méthodes oxymétriques; le degré d'anoxie constaté dans les vaisseaux périarticulaires était en rapport avec le degré apparent de l'atteinte clinique arthritique locale. L'examen régulier des malades et des témoins ne révéla pas d'anoxémie généralisée.

(3) On a trouvé qu'il était possible, oximétriquement et quantitativement, d'étalonner les lésions cutanées périphériques superficielles et les tissus périarticulaires des articulations suspectes par la présence d'anoxie locale. On discute les avantages de telles méthodes objectives d'étalonnage dans l'arthrite rhumatismale.

(4) On démontre que l'anoxie autour des articulations atteintes peut être supprimée temporairement en faisant inhaler de l'oxygène aux malades.

Anoxia Diferencial de los Tejidos y de los Órganos en la Enfermedad: Medición de los Niveles de Saturación Periarticular por Oxígeno en Artríticos

Sumario

(1) Dos métodos de oximetría fueron empleados concurrentemente para estudiar los niveles de saturación de oxígeno de la sangre arterial de la circulación general (técnica fotoeléctrica) y de los vasos periarticulares de la piel (técnica espectroscópica) alrededor de articulaciones artríticas. Los sujetos incluían 35 testigos saludables y diez enfermos con la forma reumática de atrofia artrítica.

(2) Se encontró que en los artríticos—mas no en los testigos—ocurría una divergencia en los resultados obtenidos por los dos métodos de oximetría, siendo de notar que los vasos periarticulares mostraban cierto grado de anoxia que estaba en relación con el aparente grado de desarrollo artrítico local clínico. En ninguno de los enfermos o testigos pudo encontrarse anoxemia generalizada durante el examen regular.

(3) Se encontró posible, oximétrica y cuantitativamente, el aquilatar las lesiones cutáneas periféricas superficiales y los tejidos periarticulares de articulaciones sospechosas de artritis por la presencia de anoxia local. Se discuten las ventajas que presenta un método tan objetivo para aquilatar la artritis reumatoide.

(4) Se demuestra que la anoxia alrededor de las articulaciones se puede suprimir temporalmente haciendo inhaler oxígeno a los enfermos.

PUNCH BIOPSY OF SYNOVIAL MEMBRANE*

BY

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An instrument has been devised which makes biopsy of the synovial membrane a relatively easy procedure. With this instrument the usual operative incision is unnecessary and the disability incident to operation is avoided. It has been used on 130 occasions to remove specimens from 135 joints of 108 patients, ranging in age from 3 to 71 years. Single procedures were performed on 93 patients, on the right knee 54 times, on the left knee 37 times, and on the elbow and shoulder once each. Multiple (two to six) procedures involving 42 joints were performed on fifteen patients; these entailed removal of specimens from the knees of ten patients on 32 occasions, and from both knees at one time of each of five patients (five occasions).† In the presence of sufficient distention by synovial effusion to permit safe introduction of the instrument it might also be used on the ankle or wrist joint. With added experience other applications have been found, including biopsy of bursae, diseased bone, and soft tissue masses (Bickel and Barber, 1951).

Techniques for aspiration or punch biopsy (usually for the purpose of making an early diagnosis of tumours) have been reported since about 1900, but the synovial membrane was apparently not considered among the many tissues easily accessible by such means (Franseen, 1941). A conspicuous if not isolated exception is a report by Forestier (1932), who commented on the potential value of synovial biopsy and described a modified barbed dental broach which could be inserted through the bore of a needle "to explore lymph nodes, synovia, etc.". Specimens were generally unsatisfactory however, and the procedure was abandoned (Forestier, 1951).

In July, 1948, while synovial fluid was being aspirated for inoculation into guinea-pigs because of suspected articular tuberculosis, enough synovial tissue was obtained in the tip of the needle to permit histologic diagnosis of tuberculosis. This experience led to more intensive efforts to devise an instrument whereby adequate specimens of synovial membrane could be consistently obtained. The principle of a punch technique has been utilized and in this respect the instrument resembles those used in transurethral prostatic resection. Results obtained to date justify the inclusion of synovial membrane among the tissues readily accessible to punch-biopsy procedure.

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* Read at a meeting of the American Rheumatism Association, Atlantic City, New Jersey, June 8 and 9, 1951.

† Hereafter in this paper all procedures, biopsies, or examinations performed at one time will be counted as one procedure, biopsy, examination, or instance. We shall refer to 130 procedures and 130 biopsies.

Description of the Instrument

The punch-biopsy set* consists of two main and two accessory parts (Fig. 1*a* to *d'*). There is first a hollow, round, stainless-steel tube 5 mm. ($\frac{3}{16}$ in.) in diameter, 12 cm. ($4\frac{3}{4}$ in.) in length, and 1·5 cm. ($\frac{9}{16}$ in.) in circumference (Fig. 1*a*). At one end is a flange handle marked to indicate the top (T); at the other end is a trocar point. Nine mm. ($\frac{3}{8}$ in.) from the trocar tip is an ovoid opening with a hooked lip in the end nearest the point. The aperture measures 7 mm. ($\frac{5}{16}$ in.) long and 2·5 mm. ($\frac{3}{32}$ in.) deep, and occupies the upper half of the diameter of the tube at this point. A hollow, tubular knife of the same material with a sharp, cutting rim closely fits the lumen of the outer tube (Fig. 1*b*). A stylet with a blunt end fits inside the inner tube (Fig. 1*c*). This stylet is used to push specimens out of the lumen of the tubular knife. Another stylet (Fig. 1*d*) is equipped with a sharp, hooked, corkscrew-like tip (Fig. 1*d'*), with which specimens of tissue can be extracted for examination without removal of the instrument from the joint.

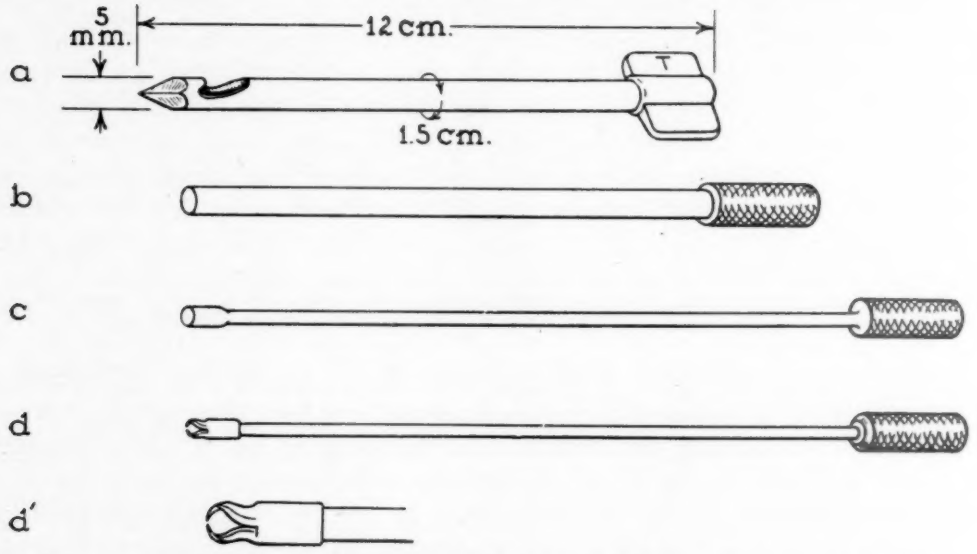


FIG. 1*a-d'*.—Set for punch biopsy consisting of two main and two accessory parts.

Technique

Punch biopsy with this instrument is performed under sterile, aseptic conditions. Soap and water, alcohol, ether, and merthiolate are applied successively to the skin in the region of the joint to be examined. Four sterile towels are draped about the joint and clamped in place. Although in our experience this procedure was carried out in the operating theatre, with similar preparation and precautions the instrument may be used outside the theatre.

Anaesthesia.—Either a general or a local anaesthetic may be used. The age and temperament of the patient, the disease present or suspected, and the severity of articular pain and tenderness, are factors to be considered in the choice of anaesthesia. In certain diseases, such as acute gouty arthritis, pulmonary tuberculosis, and disseminated lupus erythematosus, local anaesthesia would be preferred. For 130 biopsies performed on different occasions included in this report, general and local anaesthesia were used 65 times each. With adequate local infiltration of an anaesthetic agent, pain is usually experienced only momentarily, if at all, when the synovial membrane is pierced by the instrument

* Manufactured by V. Mueller and Company, Rochester, Minn., U.S.A.

or when a specimen of tissue is being cut. In no instance in which local anaesthesia was used was it necessary to resort to general anaesthesia in order to complete the procedure.

Procedure.—When a punch biopsy of a knee is to be done, a small stab wound about 1 to 2 mm. long is made over the medial or lateral aspect of the suprapatellar pouch at the upper level of the patella. The inner tube of the instrument is fully inserted into the outer tube, thus covering the opening of the outer tube. The instrument is then introduced through the stab wound and directed toward the closest superior angle of the patella. It pierces the synovial membrane at this point and traverses the articular space beneath the quadriceps ligament. At the opposite side of the joint the tip of the outer tube can be

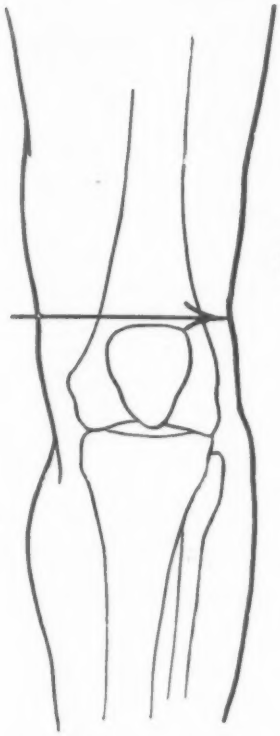


FIG. 2.—Diagram illustrating level of cross section shown in Fig. 3.

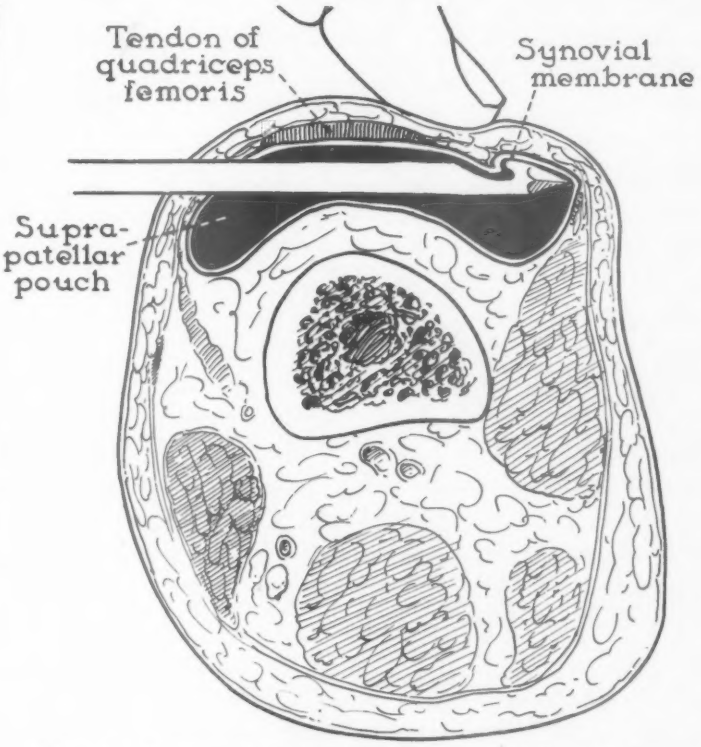


FIG. 3.—Cross section showing how synovial tissue is engaged in opening of outer tube.

palpated through the overlying skin and soft tissues. The inner cutting tube is then withdrawn sufficiently to open the aperture of the outer tube. That the instrument is in the joint space can be verified by the flow of synovial fluid out of the open end of the tube. Synovial fluid then can be collected for examination. With the inner tube withdrawn at least 1 cm., the hooked tip of the ovoid opening in the instrument is free to catch the synovial membrane. Moderate digital pressure, exerted externally on the top side of the outer tube where it is palpated in the suprapatellar pouch, facilitates the engaging of tissue in the opening (Figs 2 and 3). The inner, cutting tube is then fully re-inserted with a rotary movement to cut off the tissue engaged in the opening. The inner tube is again partially withdrawn, and the instrument is then ready to receive another specimen from the same area, or it can be moved to another place in the joint space and the same procedure repeated as many times as is desirable or necessary to obtain adequate specimens. The wound is sealed with a collodion cotton dressing, and an ace bandage is applied for 24 hours.

Specimens.—The various specimens removed collect within the lumen of the inner tube. An average of two to four is usually taken, and if desired, they can be withdrawn for examination with the corkscrew-like stylet. This is inserted and twisted clockwise several times to engage the tissue which has been cut off, and the stylet and specimen are then withdrawn. If the specimens are allowed to collect until the instrument is withdrawn, the blunt-tipped stylet is used to push out the tissue remaining within the inner tube.

Specimens of synovial membrane obtained in this way were usually 2 to 5 mm. wide and 3 to 7 mm. long. Occasionally specimens about 1 cm. long were obtained. It is desirable to obtain enough tissue to permit preparation of both frozen and fixed sections for histological examination and for tissue culture when indicated.

The technique is essentially the same for examination of other joints accessible by punch biopsy.

Post-Biopsy Morbidity

No post-operative reactions or disability have been encountered after the use of this instrument. Significant synovial bleeding was not noted in any case. In the course of these investigations this observation was confirmed by arthrotomy when feasible. No restrictions of the patient's physical activity were necessary on account of this examination. Ambulatory patients examined under local anaesthesia promptly resumed their previous activity, and physical therapy could be instituted or resumed within 24 hours.

By contrast an open operative procedure, even with antibiotics available, requires the facilities of an operating theatre, and the period of morbidity may continue for the 10 to 14 days which may be required to heal the incision. Because of this certain treatments may have to be delayed.

Punch biopsy of the synovial membrane without the operative incision and post-operative morbidity incident to arthrotomy has the advantages of minimizing discomfort, making hospitalization unnecessary, and appreciably reducing expenditure of time and money.

Analysis of Results

Sufficient synovial tissue was obtained for satisfactory histological and bacteriological examination from 112 of the 130 procedures (86·2 per cent.). In four instances (3·0 per cent.) the specimens were not considered satisfactory for histological diagnosis because of the absence of lining cells or because of insufficient tissue. No synovial membrane was obtained from fourteen (10·8 per cent.). Unsatisfactory results became fewer with increased experience, the addition of a hooked lip to the mouth of the aperture in the outer tube, and improvements in technique.

Comparison of Results of Punch Biopsy with Specimens obtained by Operative Procedures.—Eleven of the patients included in this series had an operative examination of the joint either before or after punch biopsy on the same joint. This permitted comparison of the specimens obtained by various methods. These results are shown in the Table. In all patients the specimen obtained by the punch procedure was as satisfactory for diagnosis as that obtained by the operative procedure (Figs 4, 5, and 6). In one case, although the tissue from both procedures

TABLE
COMPARISON OF SPECIMENS OBTAINED BY PUNCH AND OPERATIVE PROCEDURES ON SAME JOINT*

Case No.	Sex	Age (years)	Diagnosis	Procedure†		Interval (days)	Comment on Specimens
				First	Second		
1	M	51	rheumatoid arthritis	punch biopsy	synovectomy	0	Histologically comparable (Fig. 2). Punch biopsy would have been adequate.
2	M	49	rheumatoid arthritis	punch biopsy	arthrotomy	0	Histologically comparable. Punch biopsy would have been adequate.
3	M	61	rheumatoid arthritis	punch biopsy	necropsy	15	Histologically comparable. Punch biopsy under local anaesthesia. Death due to myasthenia gravis.
4	M	39	rheumatoid arthritis	punch biopsy	arthrodesis	76	Comparable synovitis, but neither specimen histologically diagnostic.
5	M	29	rheumatoid arthritis	arthrotomy	punch biopsy	83	Histological evidence on punch biopsy of improvement due to cortisone therapy.
6	M	37	rheumatoid arthritis	arthrotomy	punch biopsy	96	Histological evidence on punch biopsy of improvement due to ACTH therapy.
7†	M	67	tuberculosis	punch biopsy	arthrodesis	13	Histologically comparable.
8	M	18	tuberculosis	punch biopsy	arthrodesis	21	Histologically comparable (Fig. 3).
9	M	46	tuberculosis	arthrotomy	punch biopsy	55	Histologically comparable.
10	F	51	osteo-arthritis	punch biopsy	arthrotomy	11	Proliferation of superficial synovial cells and villous formation in both. Arthrotomy showed additional minimal cellular infiltration, but no focal collections of inflammatory cells.
11	M	15	osteo-chondro-matosis	punch biopsy	synovectomy	4	Grossly and histologically comparable (Fig. 4).

* Both specimens were diagnostic in all except Case 4, in which neither specimen was diagnostic.
† The right knee was examined in all but Case 7, in which the left shoulder was examined.

was comparable, the specimens were each compatible with, rather than histologically characteristic of, rheumatoid arthritis.

Definite Clinical Diagnosis before Biopsy.—The procedure of punch biopsy of synovial membrane was performed 61 times on patients with previously established diagnoses (with the patients' consent) for purposes of investigation and for study of the effects of treatment on the disease. The clinical diagnosis was confirmed in 49 of the 61 examinations (80·3 per cent.).

The diagnosis of rheumatoid arthritis was supported by the microscopical examination of the synovial tissue (Allison and Ghormley, 1931; Collins, 1949; Dockerty, 1950) removed at 33 (84·6 per cent.) of 39 procedures; no synovial membrane was removed at 5 (12·8 per cent.), and the results of the examination of tissue removed at one procedure were considered indeterminate (2·6 per cent.).

A clinical diagnosis of tuberculosis had been made in ten instances. The results of punch biopsy of the synovial membrane confirmed this diagnosis in nine (90 per cent.), and were indeterminate in one (10 per cent.).

Acute gouty arthritis was the diagnosis in six instances. The synovial membrane obtained by punch biopsy was considered compatible with this diagnosis in three (50 per cent.) (Fig. 7), no synovial membrane was obtained from two (33·3 per cent.), and the results were indeterminate in one (16·7 per cent.).

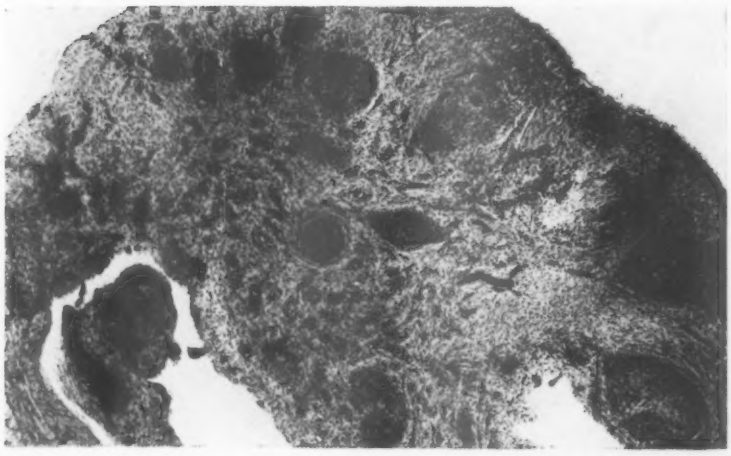
(*a*) Obtained by the punch procedure from the knee of a patient with rheumatoid arthritis.

(*b*) Obtained by arthrotomy from the same joint of the same patient just after punch biopsy was completed.

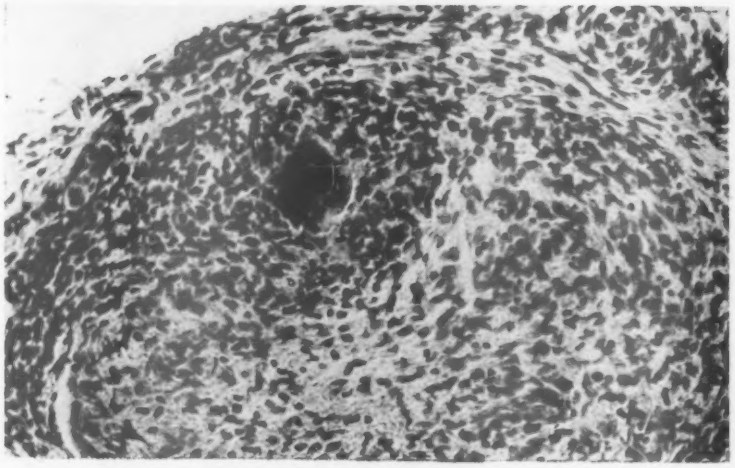
FIG. 4.—Specimens of synovial membrane (haematoxylin and eosin; × 30). They are histologically comparable and equally satisfactory for diagnosis.

A clinical diagnosis of traumatic or osteo-arthritis was confirmed in each of four instances. The results of punch biopsy in one case of dermatomyositis were indeterminate. In another case, in which a diagnosis of intermittent haemarthrosis had been made, no synovial membrane was obtained.

Indeterminate Clinical Diagnosis before Biopsy.—The diagnosis before biopsy was indeterminate in 69 instances, but with punch biopsy a definite diagnosis was established in 37 (53·6 per cent.). The diagnosis was still indeterminate after the biopsy in 32 (46·4 per cent.), including six in which no synovium was obtained.



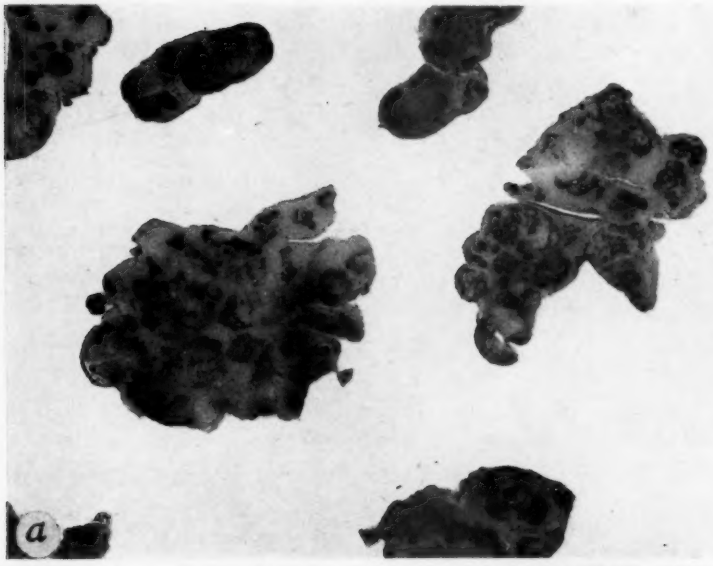
(*a*) Obtained by punch procedure from the knee of a patient with articular tuberculosis, showing many typical tubercles, including some with giant cells (× 30).



(*b*) Same specimen showing details of tubercle formation (× 200).

(*c*) Obtained in course of arthrodesis 21 days after punch biopsy (× 30).

FIG. 5.—Specimens of synovial membrane (haematoxylin and eosin). Tubercle formations similar to those noted in specimen obtained by punch procedure are seen.



(*a*) Obtained by punch procedure from the knee of a patient with osteochondromatosis. Roentgenogram of affected joint had given negative results and specimens were not obtained in fluid aspirated before punch biopsy (× 8·5).

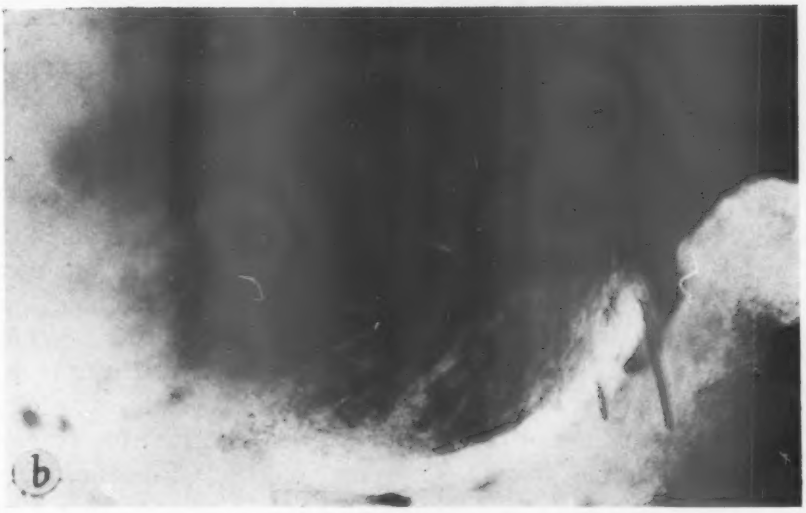
(*b*) Obtained from same joint at time of synovectomy 4 days after punch biopsy. The origin of osteochondromatous loose bodies from the synovial membrane, and the location of these formations which permitted their removal by punch biopsy, are clearly depicted (× 45).

FIG. 6.—Specimens of synovial membrane (haematoxylin and eosin).

Further analysis of this group reveals that rheumatoid arthritis was suspected clinically, but not established before biopsy, in 46 instances. The synovial specimen obtained in thirty instances (65·2 per cent.) was considered sufficiently characteristic to support the diagnosis of rheumatoid arthritis. Because of inconclusive results of biopsy the clinical diagnosis was not clarified by eleven procedures (23·9 per cent.). No synovial membrane was obtained from three (6·5 per cent.), and the synovial membrane obtained from two (4·4 per cent.) was considered compatible with a diagnosis of traumatic arthritis or osteo-arthritis.

After fifteen (65·2 per cent.) of the remaining 23 instances of synovial biopsy the diagnosis was still indeterminate, and no synovia was obtained from three

(*a*) Dark stained areas are urate deposits. Tissue was fixed in absolute alcohol and stained with haematoxylin and eosin (×35).



(*b*) High-power view showing urate crystals in typical formation at the edge of one of the areas of urate deposit seen in (*a*) (×450).

FIG. 7.—Specimens of synovial membrane obtained by punch procedure from the knee of a patient with tophaceous gout and acute gouty arthritis.

procedures (13·1 per cent.). In the five other instances (21·7 per cent.) the following diagnoses were made in one case each: synovial tuberculosis, rheumatoid arthritis, osteochondromatosis, osteo-arthritis, and normal synovial membrane. In the last instance marked obesity prevented satisfactory physical examination to determine whether any synovial inflammation was present. This and other experience indicates that normal as well as diseased synovial membrane can be removed with this instrument.

The opportunity of establishing a definite diagnosis in clinically indeterminate articular reactions is one advantage of the use of the punch biopsy.

Monarthritis.—Of the 108 patients on whom punch biopsy was performed, 26 had only a monarthritis. Diagnoses established with the aid of punch biopsy

of synovial membrane in these cases were: rheumatoid arthritis in thirteen (50 per cent.), synovial tuberculosis in three (11·6 per cent.), osteochondromatosis in one in which the roentgenograms revealed no abnormality (3·8 per cent.), and osteo-arthritis in one (3·8 per cent.). Biopsy was indeterminate in seven (27·0 per cent.), and no synovial membrane was obtained in one (3·8 per cent.). Thus, in eighteen of the 26 cases (69·2 per cent.), a diagnosis was established with the aid of punch biopsy.

Comment

Use of this relatively simple method of obtaining synovial tissue has permitted both the confirmation of clinical diagnoses and the recognition of articular disease not otherwise discernible by clinical and laboratory examinations. When the patient's history is difficult to evaluate, punch biopsy can be especially useful.

A satisfactory punch procedure produces a representative, accurate sample of either normal or diseased synovium, and can be carried out with very little inconvenience to the patient.

With easy access to synovial tissue, the various stages of different articular diseases can be studied more completely. The examination can be performed on a greater number of patients than was heretofore feasible and the same joint can be examined on repeated occasions. The same joint was examined by punch biopsy as often as six times in one patient in this series. This advantage is of considerable value in observing the response of synovial inflammation to various types of treatment (Hench and others, 1950).

When unsatisfactory, because of inadequate tissue or failure to obtain synovium, punch biopsy may have to be repeated or supplemented by an operative procedure. The ease with which a specimen may be obtained without the usual operative incision will generally offset the disadvantage of repeated biopsy or of an exploratory operation if either is indicated after punch biopsy. However, punch biopsy will not supplant arthrotomy in all instances. When a joint is explored after arthrotomy, an adequate specimen of synovium can be obtained, the articular cartilages can be examined, the absence, or extent, of panus formation can be determined, and the chance of missing a localized lesion, such as an haemangioma or tumour, is minimized. Furthermore, arthrotomy can be performed on any one of many joints, while punch biopsy is technically more adaptable to certain joints than to others. A knee joint was the site of every synovial punch biopsy reported herein except two.

Arthrotomy may still be the procedure of choice when the articular symptoms are suspected to be the result of mechanical alterations of function, and it may be necessary when punch biopsy cannot be used on the joint to be examined. On the other hand, when inflammatory or infectious articular disease is suspected in a joint suitable for the procedure, punch biopsy may be preferable.

Summary

(1) An instrument which will permit punch biopsy of synovial membrane without the usual operative incision is described. The instrument is introduced by inserting the trocar tip through a small stab wound.

(2) Punch biopsy has been performed with this instrument on 130 occasions on one or more joints of 108 patients. One or both knees were examined in 128 instances, and an elbow and a shoulder in one instance each.

(3) A sufficient specimen of synovium was obtained from 112 procedures (86·2 per cent.), and a definite diagnosis could be made in 86 instances (66·2 per cent.). Diagnoses established included rheumatoid arthritis, synovial tuberculosis, gouty arthritis, osteo-arthritis, osteochondromatosis, and normal synovium.

(4) The punch procedure described is a relatively simple method of obtaining an adequate, representative specimen of synovial tissue with little inconvenience to the patient.

We wish to express our appreciation for the assistance and technical skill received from members of the Section of Engineering of the Mayo Clinic who helped in this problem. We are indebted to Drs Dockerty, Dahlin, McDonald, and Woolner, of the Division of Surgical Pathology of the Mayo Clinic, for valuable assistance in the histological examination of the specimens obtained.

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Prélèvement au Poinçon de la Membrane Synoviale

RÉSUMÉ

(1) On décrit un instrument qui permet de prélever la synoviale au poinçon évitant ainsi l'incision habituelle. La pointe du trocart placée au bout de cet instrument s'insère par une petite perforation.

(2) Le prélevement au poinçon fut effectué 130 fois chez 108 malades sur une ou plusieurs articulations. Les deux genoux ou l'un d'eux furent examinés dans 128 cas et un coude ainsi qu'une épaule une fois chacun.

(3) Un échantillon de la synoviale de dimensions suffisantes fut obtenu après 112 prélevements (86,2%) et un diagnostic exact put être établi dans 86 cas (66,2%). Entre autres on reconnut l'arthrite rhumatismale, la tuberculose synoviale, l'arthrite goutteuse, l'ostéoarthrite, l'ostéochondromatose et la synoviale normale.

(4) Le procédé de poinçonnage décrit ici représente un moyen relativement simple pour obtenir un échantillon suffisant et représentatif de tissu synovial sans incommoder trop le malade.

Biopsia al Punzón de la Membrana Sinovial

SUMARIO

(1) Se describe un instrumento que permite la biopsia al punzón de la membrana sinovial sin recurrirse a la usual incisión operativa. La punta del trocar del instrumento se introduce por una pequeña herida perforativa.

(2) Biopsia al punzón ha sido practicada con este instrumento en 130 ocasiones, en una o más articulaciones de 108 pacientes. Una o ambas rodillas fueron examinadas en 128 oportunidades y un codo, así como un hombro, una vez cada uno.

(3) Muestras suficientes de la membrana sinovial fueron obtenidas en 112 instancias (86·2 por ciento) y diagnóstico exacto se pudo establecer en 86 cases (66·2 por ciento). Entre los diagnósticos efectuados estaban incluídos los de artritis reumatoide, tuberculosis sinovial, artritis gotosa, ósteoartritis, ósteocondromatosis y tejido sinovial normal.

(4) El procedimiento de punzar descrito es un método relativamente simple para obtener una adecuada y representativa muestra del tejido sinovial sin incomodar mucho al paciente.

SJÖGREN'S DISEASE AND RHEUMATOID ARTHRITIS

BY

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It is widely held that rheumatoid arthritis is a generalized disease in which joint symptoms are merely the most prominent feature. In support may be cited lymphocytic infiltrations and wasting of muscles, subcutaneous nodules, psoriasis, pigmentary disturbances and atrophy of the skin, changes in plasma proteins and abnormal flocculation tests, anaemia, iritis, and manifestations of general toxaemia, all of which are well known in association with the joint changes.

In view of the effects of cortisone and ACTH on many diseases which affect connective tissues, it is possible that their action in rheumatoid arthritis is due to a similar effect, and that an abnormality of connective tissue throughout the body underlies the variety of lesions which may be associated with this disease. It may be that some local stimulus such as infection, trauma, vascular disturbance, or temperature change, acting in the presence of such a generalized tissue abnormality, accounts for the manifestations in a particular case.

Further evidence supporting this view, is the observed association of arthritis of the rheumatoid type with changes in the tissues of the cornea, lacrimal and salivary glands, buccal mucous membrane, teeth, and skin.

The association of kerato-conjunctivitis sicca and joint changes was first noted by Houwer (1927), and confirmed by Isikowitz (1928); but after the publication of the detailed report of nineteen cases by Sjögren (1933) and his subsequent papers (1935, 1938) in which oral, parotid, and skin changes were also noted, the syndrome has become known as Sjögren's disease.

Weber (1945) and Weber and Ellman (1949) have reviewed the literature and described further cases, one of which also showed changes in the respiratory tract. Stenstam (1947) and Holm (1949) have described detailed investigations in a large series of cases in Sweden.

Sjögren considered that the syndrome was a disease *sui generis*, but Weber thought the manifestations were merely the local symptoms of a general disease. In support of the latter concept, may be quoted Holm's finding that 53 of 440 patients with rheumatoid arthritis had objective evidence of kerato-conjunctivitis sicca, although many of the 53 did not complain of symptoms related to the eyes. He infers that the ocular changes are relatively common in ordinary cases of rheumatoid arthritis. The objective tests for kerato-conjunctivitis sicca used

by Holm were the same as those used by Sjögren—the rose bengal staining method to demonstrate denudation of the corneal epithelium, and the test described by Schirmer (1903) to assess the efficiency of lacrimal secretion.

If Holm's conclusion can be substantiated, it provides further evidence that the joint symptoms of rheumatoid arthritis are local processes superimposed upon a tissue disorder widespread throughout the body.

We have carried out Schirmer's test in a small series of rheumatoid arthritis patients and the results are reported below, together with the clinical and autopsy details of a case of Sjögren's disease showing unusual changes in the renal tracts.

Investigation

Material.—The series comprised 47 women and fifteen men, aged 17 to 72. All had typical manifestations of rheumatoid arthritis. The control group also comprised 47 women and fifteen men, of comparable ages, who were hospital in-patients suffering from non-rheumatic illnesses. None of the subjects suffered from ocular symptoms.

Method.—Strips of red litmus paper 5 × 33 mm., were folded at right angles 3 mm. from one end, and the folded end was tucked into the outer canthus of the lower conjunctival sac. The length of paper which became wet in 5 min. was measured and the average for the two eyes recorded. Litmus paper from the same batch was used throughout.

Schirmer, Sjögren, and Holm all considered a moistened area 15 mm. long to be the lower limit of normal.

Results.—These are shown in the Table. Of the rheumatic subjects, seventeen of the 47 women, and three of the fifteen men had deficient lacrimal secretion by this standard, compared with four of 47 women and one of fifteen men in the control group. The observations show a significant difference between the rheumatic and non-rheumatic subjects ($\chi^2 = 9{\cdot}8$, D.F. = 1, $P < 0{\cdot}01$) and thus support the conclusions of Holm. The length of paper moistened bore no relation to age.

TABLE

RESULTS OF SCHIRMER'S TEST IN TWO SERIES OF 62 CASES

Result (mm.)	Cases	
	Rheumatoid	Control
0-4	2	1
5-9	8	1
10-14	10	3
15-19	9	9
20-24	9	11
25-29	14	25
30	10	12

Report of One Case

Clinical Observations.—The patient (R.I. No. 18667/43) was a married woman who was first admitted to the Radcliffe Infirmary in July, 1948, at the age of 28. Her presenting symptoms were pain and stiffness of the joints for 3 months. The condition had started in her right knee and had spread to the left knee, shoulders, elbows, wrists, and fingers.

For the same period she complained of weakness and pain in the muscles about the affected joints. Her general health had deteriorated, she was pale, had lost weight, and was always tired. For 10 years she had noticed excessive thirst and polyuria. The thirst was associated with chronic dryness of the mouth so that she had to drink copiously with her meals in order to masticate her food. She associated this with a series of parotid swellings, the first of which occurred at the age of 19 on the right side. There had been seven further swellings on the left side, the last having occurred in 1946. The first swelling was thought to be suppurative and was incised, but the rest all subsided spontaneously.

She did not complain of any ocular symptoms, but on direct questioning said she had occasional attacks of soreness of the eyes, and then volunteered that she was frequently troubled with sticky mucus between the lids.

There were no other symptoms referable to the alimentary or urinary systems, and none referable to the respiratory, cardiovascular, or central nervous systems. Her menstrual periods were normal and did not appear to be associated in any way with her symptoms.

She had had two pregnancies. The first (1941) was normal; the second (1947) was complicated by puerperal septicaemia. The arthritis commenced 8 months after the second pregnancy. There had been no previous rheumatism, renal disease, or other significant illness. The family history was not relevant.

On examination she was a pale, thin, tired-looking woman, with dry skin and dry falling hair. There was tenderness and fusiform swelling of the proximal interphalangeal joints. She could barely close her fist. During the period of observation, varying degrees of pain, swelling, stiffness, and restricted movement occurred in the wrists, elbows, shoulders, and knees. There were several subcutaneous nodules over the right ulnar surface and the right patella.

All her teeth had been extracted some years previously. There was some redness and smoothness of the mucous membrane of her tongue, but no apparent abnormality of the buccal mucous membrane nor of the salivary glands. Her eyes appeared normal. There were enlarged lymph glands, about 1 cm. in diameter in both axillae, but none elsewhere.

The thyroid gland was not palpable, and there was no evidence of thyroid dysfunction. Blood pressure was normal (120/65 mm.) and there was no abnormality of cardiovascular, respiratory, alimentary, or central nervous systems. Liver, spleen, and kidneys were not palpable.

Investigations showed a moderate hypochromic anaemia (haemoglobin 9·6 gm. per 100 ml.), leucocytes 9,000 per c.mm., erythrocyte sedimentation rate (Westergren) 68 mm. in one hour. Urine contained 20 mg. protein per 100 ml., but no other abnormal constituents. Blood urea was 46 mg. per 100 ml., plasma protein 7·5 gm. per 100 ml. (albumin 3·6, globulin 3·9), serum alkaline phosphatase 6 King Armstrong units.

The clinical picture was that of mild rheumatoid arthritis associated with rather more constitutional disturbance than one would have expected from the joint changes. In view of the recurrent parotid swellings, dryness of mouth, dry skin, dryness of eyes, dental deficiency, and arthritis, she was considered to be a case of Sjögren's disease. During her stay in hospital there was some improvement in her general condition, but the arthritis remained unchanged and she was discharged to continue under observation as an out-patient.

For the next 2 years there was little real change in her condition. For most of the time she was tired and lacking in energy, and her arthritis never completely settled down. Haemoglobin varied from 8·8 to 13·1 gm. per 100 ml., and erythrocyte sedimentation rate from 8 to 42 mm. in one hour. The proteinuria increased after her discharge, and varied from 40 to 90 mg. per 100 ml. No formed elements were found in her urine. In April, 1949, blood urea was 38 mg. per 100 ml.

In May, 1949, intravenous pyelogram (Figs 1 and 2) was carried out by Dr. J. L. Boldero, of the *X*-Ray Department of the Radcliffe Infirmary, to whom we are indebted for the following report:

> Preliminary renal *x* rays: Multiple calcified glands in the lower abdomen. There are punctate calcifications overlying both kidney shadows (Fig. 1).
>
> Excretion urography: Good concentration of dye on both sides. The presence of the punctate calcified shadows is closely associated with all the calyces (Fig. 2). The aetiology of the calcification is quite obscure.

FIG. 1.—*X* ray taken during life, showing small calcified deposits in pyramids of both kidneys.

FIG. 2.—*X* ray taken during life, lateral view.

At this time her serum phosphate was 4·5 mg./100 ml., calcium 7·8 mg./100 ml., and phosphatase 7 King-Armstrong units. Blood pressure was 110/70 mm.

Thirst and dryness of the mouth also ran a variable course, and for periods her salivary secretion appeared to be normal. There was no recurrence of parotid swelling. A series of Schirmer's tests carried out over 12 months gave the following results:

Date	*Average length moistened (mm.)*
15.7.49	6
14.9.49	15
26.9.49	16
23.11.49	8
5.7.50	5

Treatment during this period was along symptomatic lines, with physiotherapy, salicylates, ferrous sulphate, and a short period at a spa.

In June, 1950, the patient complained of increasing joint symptoms, especially in the shoulders and neck, and of increasing fatigue; she was noted to

have lost about 4 lb. weight in the previous 3 months. During the next month symptoms persisted and she lost a further 5 lb. Physical examination on several occasions showed a chain of tender lymph glands over the anterior border of the left trapezius muscle but no other fresh abnormality. Erythrocyte sedimentation rate 44 to 50 mm. in one hour, haemoglobin 11·8 gm./100 ml., white blood count, 4,500 c.mm., urinary protein 40 mg./100 ml. Chest *x* ray showed no lesion.

This was the last time we saw the patient alive. Before her next appointment at the out-patient department was due she developed an acute attack of gastro-enteritis with fever, vomiting, and diarrhoea, and was admitted to the local cottage hospital. Symptoms persisted, and she developed pleural and pericardial friction rubs. Re-admission to the Radcliffe Infirmary was arranged, but on the same day her condition suddenly deteriorated, and she died on October 3, 1950.

Autopsy Findings.—*Post-mortem* examination was performed 24 hours after death. The body was that of an emaciated woman appearing older than 30 years. There was slight fusiform swelling of the proximal interphalangeal joints of both hands. The skin was natural and no subcutaneous nodules were found.

No lesions were found in the skull, meninges, brain, or cerebral vessels, and there were no lesions in the middle ears, mastoid cells, or paranasal sinuses.

The mouth was edentulous. The tongue was red and dry but showed no ulceration. There was some ulceration of the soft palate. The lower respiratory passages appeared natural but contained some viscid muco-pus.

Both lungs were adherent on all surfaces to the chest wall, due to the presence of a thin layer of plastic fibrinous exudate. The visceral pleura did not appear congested. The major part of both lungs was well aerated, but there were small patches of collapse along the lower margin of the lower lobes. Emphysematous bullae up to 1 cm. in diameter were scattered over the surfaces of both lungs. There was no excess of fluid on section. About half a dozen small areas of consolidation (up to 3 mm. in diameter) were found in the periphery, mostly in the right lung. Their margins were dull red and the centres yellowish. There was no gross abscess formation.

The only change in the cardiovascular system was a dry fibrinous pericarditis.

Only the left parotid gland was examined and this appeared smaller and more fibrinous than usual. The oesophagus, stomach, and small intestine appeared natural. The transverse colon showed some punctate ulceration. The liver appeared paler than usual with some fatty change. The gall bladder, bile ducts, and pancreas appeared natural.

The kidneys were both slightly smaller than natural. The cut surface showed some pallor, and the cortex was poorly differentiated from the medulla. The pyramids contained numerous yellowish-brown, stony-hard concretions up to 1 mm. in diameter. The pelves contained no stones and the rest of the urogenital tract appeared natural.

The breasts were atrophic. The spleen was slightly enlarged and the follicles prominent. There was slight generalized lymph-gland enlargement.

The left knee contained a slight excess of fluid and the synovium was thickened and congested.

Histology.—The findings are grouped into:

(*a*) Those related to the terminal illness with pneumonia and renal failure.
(*b*) Those related to the chronic condition in the lacrimal and salivary glands, joints, and muscles.

(*a*) The kidneys show generalized tubular dilatation. There are numerous narrow wedge-shaped lesions in the cortex, in which the glomeruli show capsular fibrosis and

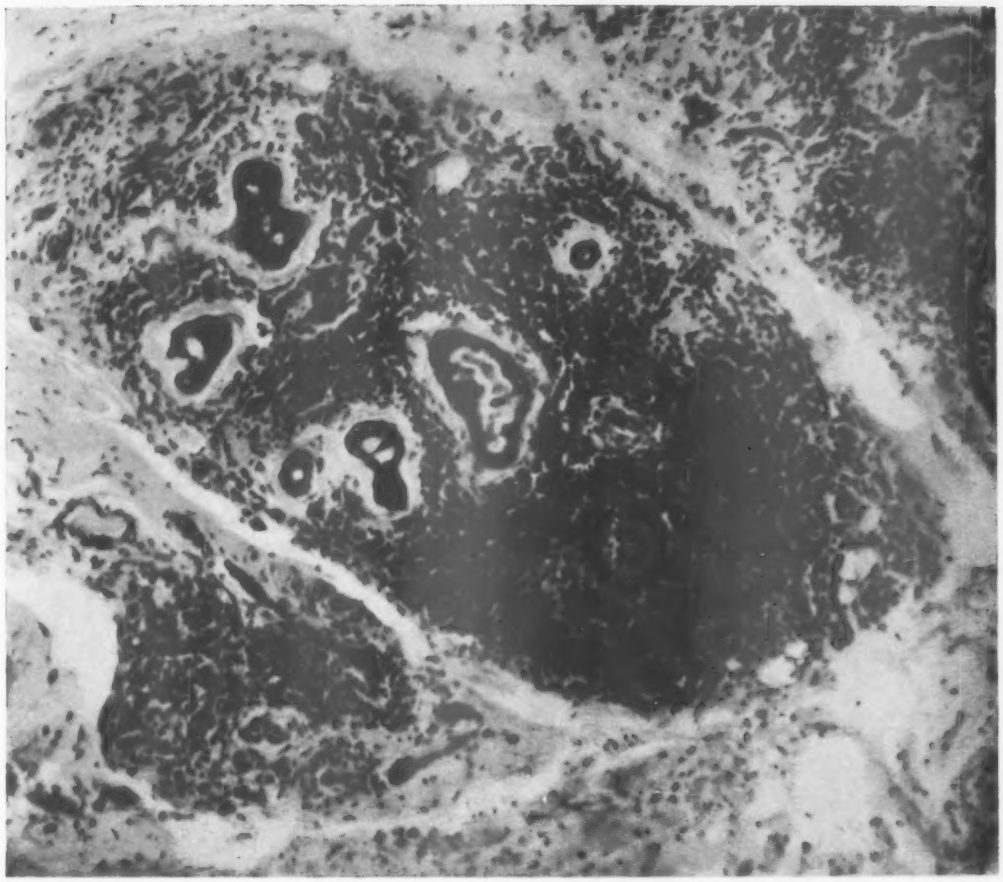

FIG. 3.—Section of lacrimal gland taken at *post-mortem*, showing extensive infiltration with lymphocytes and plasma cells with disappearance of gland acini. The ducts are relatively unaffected. There is also some perilobular fibrosis. Haematoxylin and eosin ×120.

obliteration, and there is fibrous replacement of the tubules with some lymphocytic and plasma-cell infiltration. The concretions in the medulla lie in the collecting tubules. There are no vascular lesions.

The pleura and pericardium show subacute inflammatory change with exudation of fibrin as seen in uraemia. Most of the major bronchi show severe subacute inflammatory change. The areas of consolidation are related to branch bronchi and consist of acute inflammatory exudation with central necrosis.

The gastro-intestinal tract shows some lymphocytic and plasma-cell infiltration of the mucosa. Autolysis prevents detailed examination, but there appear to be no underlying chronic changes. There is some lymphocytic and plasma-cell infiltration of the portal tracts of the liver, and some centrilobular fatty change.

(*b*) The right lacrimal gland (Fig. 3) shows chronic inflammatory change. This is patchy in distribution, and resembles that described by Sjögren (1933). Some of the lobules appear natural, others show a moderate degree of lymphocytic and plasma-cell infiltration between the acini. Many acini in these lobules are made up of irregular pale cells which have lost their orderly arrangement. Mitoses are seen occasionally but there are no cell inclusions. In the most severely affected lobules the acini have disappeared, leaving only the ducts surrounded by lymphocytes and neutrophile leucocytes and some young

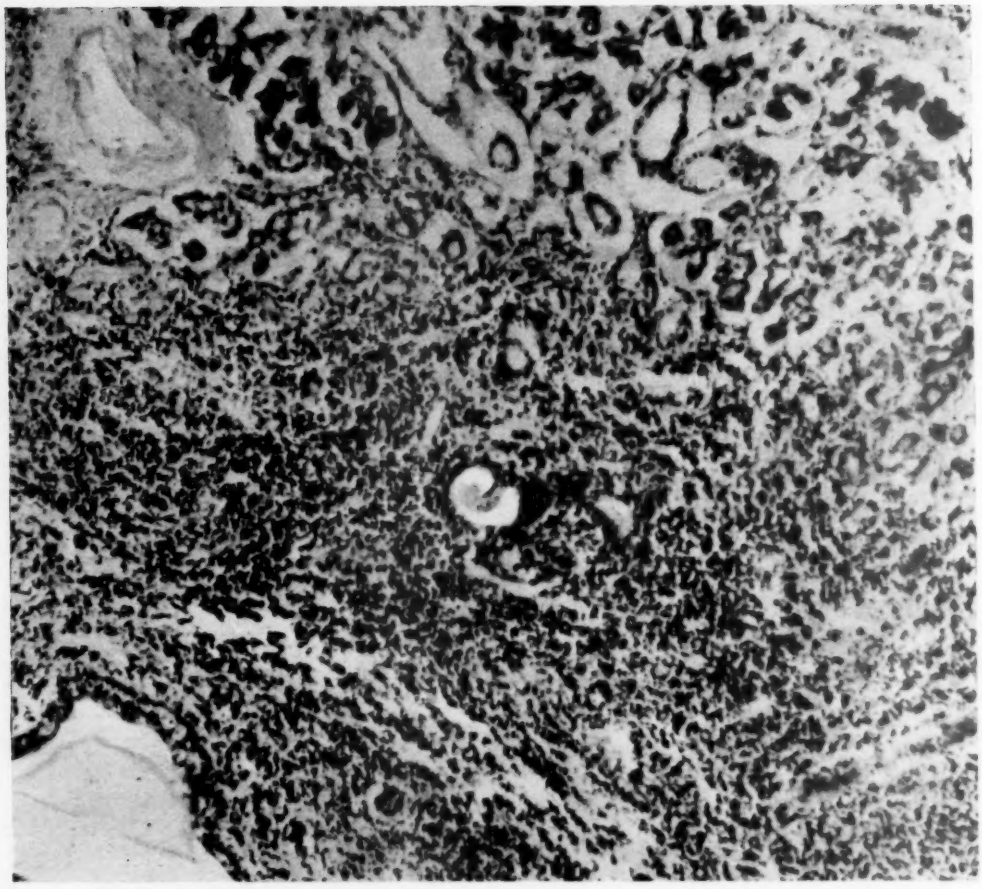

FIG. 4.—Section of parotid gland taken at *post-mortem*, showing similar extensive replacement of gland acini by lymphocytes and plasma cells. Haematoxylin and eosin ×120.

fibrous tissue. Some of the ducts are distended with inspissated material. About a third of the gland substance appears capable of normal function. The overlying conjunctiva shows cellular and pericellular oedema of the stratified epithelium, with some cyst formation and dilatation of the underlying lymphatics. This change was described by Sjögren in his biopsy material.

Sections of the parotid and submandibular glands show changes similar to those in the lacrimal gland but more severe and more extensive. There is advanced fibrosis and some of the lobules show replacement by fatty connective tissue. The parotid (Fig. 4) shows many cystic spaces lined by flattened-duct epithelium and filled with inspissated mucus.

The submucous glands of the nasal mucosa, pharynx, tongue, trachea, and bronchi show similar changes which are most marked in the soft palate (Fig. 5), where areas of epithelium have been replaced by necrotic material and poorly formed granulations. The mucosa of the paranasal sinuses is natural and there are also isolated lobules of mucus-secreting glands showing no abnormality in otherwise severely affected areas. The mucosa of the pharynx shows a range of changes ending in ulceration. There is prolongation of the rete pegs with acanthosis and considerable variability in the basal epidermal cells with some mitotic activity, and in the ulcerated areas there has been a disappearance of the superficial epithelium and irregular regeneration of the basal cells. In the pharynx the

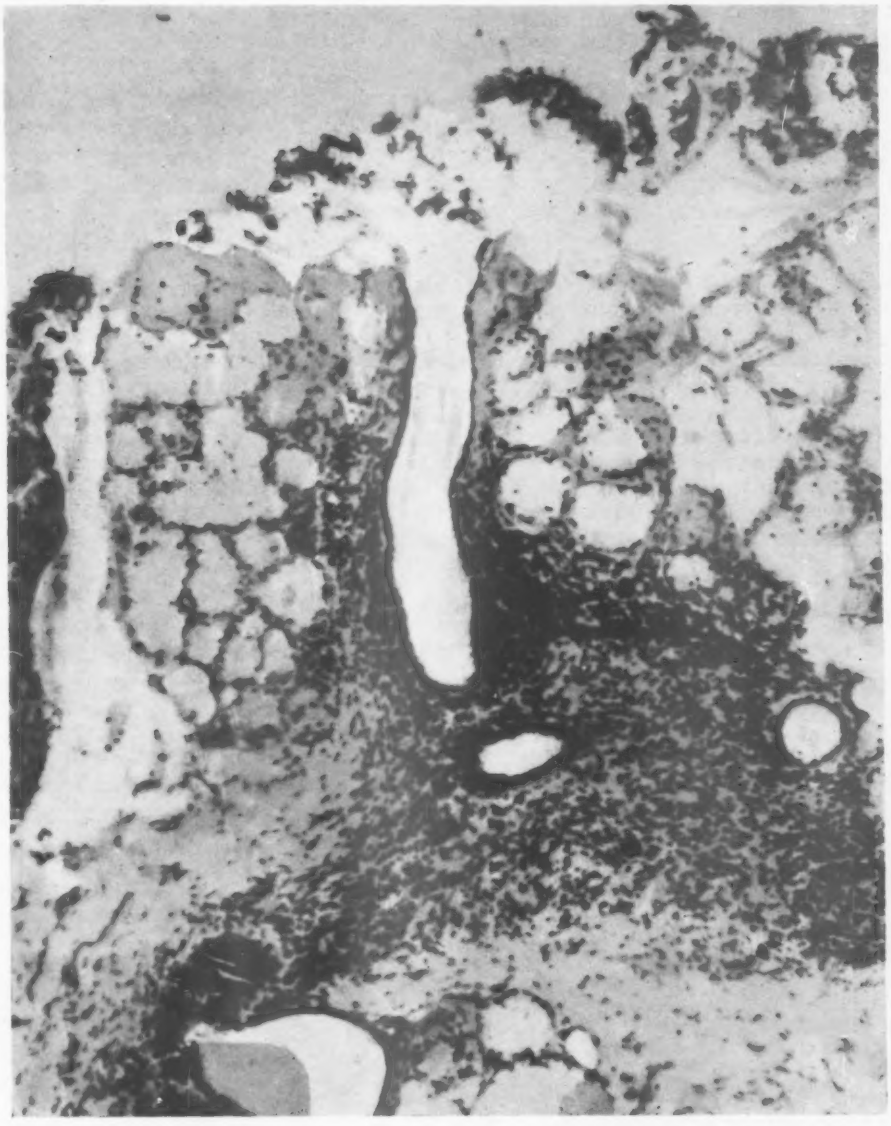

FIG. 5.—Section from soft palate taken at *post-mortem*, showing necrosis of superficial mucosa and inflammatory changes in submucous glands. Haematoxylin and eosin ×120.

ulcerated areas are covered by a fibrinous membrane in which there is a mixed bacterial and fungal flora. In the non-ulcerated areas, best seen in the tongue, there is a lymphocytic proliferation of the subepithelial connective tissue. The glands of the uterine cervix are natural. The thyroid, pancreas, and skin show no abnormality.

Section of the left fourth interphalangeal joint shows some marginal erosion of the joint cartilage, with the formation of a relatively acellular fibrous pannus. Similar fibrosis without marked inflammatory cell infiltration is seen in the synovium. The synovium of the knee joint shows oedema and proliferation of the villi, with a minor degree of lymphocyte and plasma-cell infiltration.

A section from the left quadriceps extensor muscle of the knee shows perineural and perivascular foci of lymphocytic and plasma-cell infiltration, with some proliferation of fibrous tissue.

The lymph nodes show moderate medullary and sinus proliferation, and in a node from the right cervical chain there is medullary reticulum-cell proliferation with some binucleate forms.

The cerebrospinal fluid urea content was 145 mg./100 ml. The renal medullary concretions were composed of calcium and magnesium phosphate.

Summary of Autopsy Findings.—It is evident that the patient died with uraemia and aspiration pneumonia with abscess formation, probably precipitated by an attack of non-specific enteritis. The kidneys were the site of a chronic low-grade pyelonephritis which had not been severe enough to cause renal failure until the final acute illness with its disturbance of fluid balance.

The cause of the concretions in the tubules remains obscure. They had been present for many months if not years, and in view of the history of polydipsia and polyuria, cannot be related to dehydration. There was no clinical, biochemical, or autopsy evidence of parathyroid tumour.

The changes described by Sjögren were present in the lacrimal glands and the conjunctiva, and were even more marked in the salivary glands and respiratory mucous membrane. Histological changes characteristic of rheumatoid arthritis were present in the joints. Although Weber (1945) suggested that the chronic inflammatory process may also occur in the pancreas, thyroid, skin, colon, and genital tract, there was no evidence of involvement of these tissues in the present case.

Discussion

Our observations have confirmed those of Holm (1949) that patients suffering from rheumatoid arthritis tend to have a deficiency of lacrimal secretion even though there are no symptoms referable to the eyes.

It would be interesting to examine the lacrimal and salivary tissues in a series of rheumatoid arthritis cases coming to autopsy, to determine whether the histological changes are also present in asymptomatic cases. It may be that these non-specific inflammatory lesions occur in these glands and respiratory tissues, as they do in skin (Curtis and Pollard, 1940), muscles (Freund and others, 1945; Steiner and others, 1946; Gibson and others, 1946), tendons (Kellgren and Ball, 1950), and subcutaneous tissues (Bennett and others, 1940). The changes described above resemble in many ways those reported by the above workers: the lymphocytic and plasma-cell infiltrations, the disorganization of the underlying tissue with necrosis in some areas, and the rather feeble fibrous tissue response.

Further evidence that the lacrimal and salivary lesions are aetiologically related to the rheumatoid process is the clinical observation that the ocular and oral signs in a case of Sjögren's disease cleared up along with the joint lesions on treatment with ACTH, and relapsed again on cessation of therapy (Stephens, 1950).

The relationship of the chronic renal lesion to the salivary, lacrimal, and respiratory lesions in our patient is not clear. Probably the chronic pyelonephritis was quite coincidental, and the tubular calculi were secondary to the chronic infection. The possibility of a more direct relationship, however, cannot be excluded.

Summary

(1) Clinical and autopsy observations in a case of Sjögren's disease are described.

(2) An investigation of the lacrimal secretion in a series of patients confirms

the observations of Holm (1949) that there is a tendency to deficient secretion in rheumatoid arthritis.

(3) The importance of the lacrimal and salivary lesions is discussed in relation to the aetiology of rheumatoid arthritis.

Our thanks are due to Dr. F. V. Squires of Wantage for details of the patient's final illness and for his co-operation in arranging for the autopsy, and to Dr. A. H. T. Robb Smith for his advice on the histological examination. We are also indebted to Dr. R. H. Cowdell of the Department of Pathology, Radcliffe Infirmary, for the photomicrographs.

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La Maladie de Sjögren et l'Arthrite Rhumatismale

RÉSUMÉ

(1) On présente l'observation, y compris les résultats d'autopsie, d'un cas de maladie de Sjögren.

(2) L'étude de la sécrétion lacrymale chez un groupe de malades confirme les observations de Holm (1949) constatant que dans l'arthrite rhumatismale cette sécrétion tend à diminuer.

(3) On discute l'importance des lésions lacrymales et salivaires par rapport à l'étiologie de l'arthrite rhumatismale.

La Enfermedad de Sjögren y la Artritis Reumatoide

SUMARIO

(1) Se presenta un informe clínico y de autopsia de un caso de enfermedad de Sjögren.

(2) El estudio de la secreción lacrimal en un grupo de enfermos confirma las observaciones de Holm (1949) de que en la artritis reumatoide esta secreción tiende a ser deficiente.

(3) Se discute la importancia de las lesiones lacrimales y salivarias en relación con la etiología de la artritis reumatoide.

SPONTANEOUS RUPTURE OF THE TENDON OF EXTENSOR POLLICIS LONGUS AS A COMPLICATION OF RHEUMATOID ARTHRITIS

BY

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Numerous authors have recently stressed the frequent clinical evidence of tendon involvement in rheumatoid arthritis. Edström (1945) found evidence of " tendinitis ", or " peritendinitis ", in 48 per cent. of 391 cases of chronic rheumatic polyarthritis. The long flexors to the fingers were involved in 38 per cent. of his cases, and the extensors in 10 per cent. Kellgren and Ball (1950) analysed 100 of their own cases, and found tendon lesions present in 42, in 37 of which the long flexors of the fingers were affected. Other tendons described as clinically affected were the extensors of the fingers, the tendons around the ankle, and Achilles' tendon, but no mention was made of the extensor pollicis longus. Fifteen of their cases were explored, and the clinical findings confirmed at operation. They emphasized that in most cases of rheumatoid arthritis the tendon lesions were only one aspect of " a generalized process involving joints, muscles, and occasionally viscera ", but that in rare cases the tendon lesions may be the chief cause of disability. The disabilities described were snapping fingers (Helweg, 1924; Sperling, 1949, 1950; Kellgren and Ball, 1950), weakness of grip (Edström, 1945), and inability to clench the fist. No cases of rupture of tendon were quoted, nor was this described as a possible occurrence.

Kersley (1948), in a short paper, described two cases of spontaneous muscle rupture occurring in rheumatoid arthritic subjects. No similar cases have been described elsewhere. In his first case, the muscle ruptured was in the calf (? gastrocnemius); in the second, multiple lesions were described. In addition to the rupture of the quadriceps, which appeared to be at the musculo-tendinous junction, there were spontaneous ruptures of the extensor apparatus of the fourth digit of the right hand, and the flexor digitorum profundus of the third digit of the left hand. The patient's description of the spontaneous rupture of the extensor digitorum was " a slight pain, like an electric shock, running up the forearm ". The site of these lesions was considered to be in the forearm, probably at the musculo-tendinous junction.

Both these cases were males, one aged 56, the other 54. In the first case, a typical rheumatoid arthritis had been present for one and a half years, in the second the quadriceps rupture occurred two years after the onset of the disease, the extensor rupture a further one and a half years later.

Platt (1931), discussing tendon ruptures, described two groups:

(*i*) A common type, produced by the sudden powerful over-stretching of a muscle already in a state of contraction.

(*ii*) A less common form—spontaneous rupture—seen in certain tendons which occupy bony grooves.

He considered the tendons most likely to rupture to be the extensor pollicis longus and the long head of the biceps. The spontaneous rupture of the extensor pollicis longus occurred as an isolated lesion, e.g. " kettledrummers' palsy " (Von Zander), generally preceded by a painful tenosynovitis caused by prolonged use of the drumstick—or associated with a fracture, usually of the Colles type. In this group, the tendon rupture takes place some weeks after the occurrence of the bony injury, and the " sequence is fracture, distortion of the tendon groove, adherence of the tendon, attrition, rupture ". Of the seven cases he described, one followed an occupational tenosynovitis, and six were associated with a fracture of the lower end of the radius.

Platt considered the diagnosis of rupture of the extensor pollicis longus tendon depended on the following signs:

(*i*) Inability to extend the dropped terminal phalanx of the thumb against resistance.

(*ii*) Absence of the subcutaneous bowstring normally formed by the tendon when the thumb is fully extended.

He also noted these two additional points:

(*iii*) It is sometimes possible to feel the distal part of the divided tendon.

(*iv*) The loss of function may be demonstrated by stimulating the muscle belly by a faradic current.

McMaster (1932, 1933) considered that in all cases of spontaneous rupture of the extensor pollicis longus there was a pre-existing tendon disease or injury. The commonest causes were a chronic tenosynovitis, which occurred in drummers, and as a late sequel of Colles fracture. For the latter, he considered the cause was either a partial severance at the time of injury, or a local tendon necrosis caused by injury to the blood supply of the tendon at the time of fracture. Pathological conditions predisposing to tendon rupture included tuberculous tenosynovitis, gonococcal tenosynovitis, syphilis, and tendon tumours. From a series of experiments on rabbit tendon, in which he determined the tensile strengths and points of rupture of normal, crushed, partly-severed, and resutured tendons, and tendons ligatured so as to obstruct their blood supply, he concluded:

Normal tendons do not rupture. Instead, the tendon insertion or muscle origin gives way, or the muscle belly ruptures, or the musculo-tendinous junction separates, or the bones fracture.

In addition he found that obstruction of the blood supply of the tendon gave rise to a spontaneous rupture at the site of obstruction in about four weeks, even when the tendon sheath had been replaced carefully.

Cases Previously Reported

(1) Von Stapelmohr (1940) surveyed the literature on spontaneous rupture of the extensor pollicis longus, and analysed 148 cases, the total he was able to find recorded, including his personal series. He quoted Pirker (1934) as considering that rheumatic infections

were of significance in causing a mesotendinitis and paratendinitis predisposing to the rupture, but the detailed analysis of the 148 cases included only one in which a polyarthritis of the rheumatoid type was present. Two-thirds of the cases were in women, and the age varied between 16 and 74. The right hand was slightly more commonly involved than the left (68 : 56). In some cases the rupture was preceded by a crepitant tenosynovitis. The case history of the one " rheumatic " subject was as follows:

A dental mechanic aged 25 had a polyarthritis which followed a carditis at age 8. Both wrists were involved. Without any history of local trauma, he suddenly lost extension of the right thumb. *X* ray showed decalcification of the hand and loss of cartilage of the thumb and wrist. At operation, rupture of the extensor pollicis longus was found *située distale à la coûture du carpe*. It was impossible to repair the tendon by direct suture, and the distal end was inserted into the extensor carpi radialis brevis. No microscopic examination was made.

(2) Wadstein (1946), in a paper on spontaneous rupture of the tendon of extensor pollicis longus, described the condition as being rare, both absolutely and in relation to other very common injuries of the wrist. He quoted von Stapelmohr as seeing three out of 1,250 injuries of the wrist *x* rayed at Norrköping Hospital from 1927 to 1937, of which 1,000 were fractures of the radius; Moore as seeing three out of 500 fractures of the radius; and Oppolzer as seeing two out of 800 fractures of the radius. He himself described two cases seen personally; one, which he considered to be due to " rheumatism ", is described as follows:

A male, aged 37, was " always perfectly healthy, and never had any pains in the joints ". Two months before admission to hospital, he had pain and swelling of the left wrist, which gradually improved. Five weeks later he noticed suddenly that he was unable to extend the left thumb. Examination of the left wrist and forearm showed no signs of inflammation or muscle atrophy. The Wassermann reaction was negative, and the erythrocyte sedimentation rate was 18 mm., falling to 9 mm./hr. in a week. *X* ray of the hand was negative; clinically there was a 45° loss of extension of the thumb, and the tendon of the extensor pollicis longus did not appear in the snuff-box.

A nerve injury was suspected, and " neuritis " was diagnosed by a neurologist; however, the wrist was explored and at operation the tendon was found divided, the ends being widely separated. Both ends were thickened, oedematous, and degenerate, but the muscle showed no gross abnormality. A tendon transplant of the extensor indicis was performed, with excellent functional results. The pathologists' report was as follows:

A chronic tendinitis. In the middle of the tendon as well as on its outer part are nests of granuloma. There are no certain signs of anything extraordinary, but rheumatic granulation may be surmised.

Wadstein accepted this report, but commented:

It may seem surprising that a man quite healthy in other respects should get a rheumatic affection only in this part of the body !

(3) Only one case of bilateral rupture of the extensor pollicis longus is fully described in the literature (Andreasen, 1934):

After a motor-cycle accident, a man of 30 injured both wrists. One tendon ruptured 5 days later, and the second after a further 10 days.

Von Stapelmohr (1940) refers also to another case, but gives no details. Thus bilateral spontaneous rupture of the extensor pollicis longus tendon without any previous injury does not appear to have been described in medical literature.

Present Series of Cases

In view of the apparent rarity of spontaneous rupture of the extensor pollicis longus, its occurrence in a series of cases of rheumatoid arthritis seems worth reporting. The following five cases were observed between April, 1949, and April,

1951. Case 3 was seen at the Royal National Hospital for Rheumatic Diseases, Bath, by permission of Dr. G. D. Kersley. Cases 4 and 5 were not personally seen by the author.

Case 1.—A civil servant, aged 43, had a typical generalized rheumatoid arthritis of five years' duration, involving hands, wrists, shoulders, feet, and knees. He was Stage III, Class II, by the classification of Steinbrocker and others (1949). The erythrocyte sedimentation rate was 20 mm. and the Wassermann reaction negative. He was right-handed.

Whilst gardening he suddenly noticed the whole right thumb " went into a cramp ". Five minutes later he noticed that he had lost extension of the terminal phalanx of this thumb. Thirty minutes later he felt a tightness in the mid-forearm. Two weeks later while taking off a pullover, he felt a sudden cramp in the muscles of his left forearm, and immediately noticed that the left thumb had become flexed at the terminal phalanx, and that he had lost the power of active extension there. He was seen in the Out-patient Department of Leeds General Infirmary two weeks later. He had no disability other than a loss of power of extension of the terminal phalanx of both thumbs, which were held in about 30° of flexion. Both wrists were thickened. All Platt's criteria were present on both sides. Typical rheumatoid deformities of the fingers were present. A palpable mass was present in the left forearm $2\frac{1}{2}$ in. proximal to the radial styloid, which moved on attempting extension of the thumb. The tendon of extensor pollicis longus could not be demonstrated as a boundary to the snuff-box on attempting thumb extension against resistance. The findings were identical on the right side.

Radiographs of the wrist showed some osteo-porosis of the bones of the hands and wrists, with some cystic changes present in the right carpus. No hypertrophic bone was seen on the dorsum of the radii and there was no evidence of old fractures or deformities.

Faradic stimulation was applied to individual forearm muscles by a small electrode. The mass previously observed could be felt to move proximally when the muscle contracted, but no extension of the terminal phalanx of the thumb could be obtained.

Operation was refused by the patient as function was good. Six months later his rheumatoid arthritis had settled considerably, after a long course of gold injections. The condition of the thumbs was unchanged.

Case 2.—A textile worker, aged 45, doing a skilled manual job, had a history of rheumatic fever when aged 17. He developed a typical generalized acute polyarthritis of the rheumatoid type 18 months before the tendon rupture, involving the hands, wrists, feet, and knees. He was receiving in-patient treatment at the Royal Bath Hospital, Harrogate, and had had courses of both gold and copper, in addition to extensive physiotherapy. He was right-handed.

One day whilst unknotting the string round a small parcel, he felt a sudden pain on the dorsum of the left wrist, and up the forearm. He then noticed that " his thumb had dropped into the palm of his hand ", and then he was unable to extend it. A plaster splint was applied within three hours, with the thumb extended. Twelve hours later he felt a sudden pain " like an electric shock " in the thumb. On examination next day, he was seen to be a rather wasted man, with a severe general and active rheumatoid arthritis. His hands, wrists, and knees were severely involved, although there was no ankylosis of the joints, and no fixed deformity of the fingers. He was Stage III, Class III, by the Steinbrocker classification. His erythrocyte sedimentation rate was 46 mm. and his Wassermann reaction negative. Active extension of the terminal phalanx of the left thumb was absent, and when unsupported this fell into 45° of flexion. The tendon of extensor pollicis longus was not palpable at the wrist when an attempt was made to extend the thumb. The proximal end of the tendon could not be felt. Radiographs of the wrist showed no abnormality other than osteo-porosis. A diagnosis of spontaneous

rupture of the extensor pollicis longus was made, and confirmed at operation 10 days later (Mr. H. Petty). The tendon of the extensor pollicis longus was found divided proximal to the level of the groove in the radius. The proximal end had retracted well up the forearm. Direct repair was not possible. Transplantation of the tendon of extensor carpi radialis brevis to the distal end of the tendon of the extensor pollicis longus was performed with excellent functional results. The proximal portion of the tendon, along with some of the muscle was removed for histological examination.*

Nature of Specimen.—Ruptured tendon of extensor pollicis longus.

Macroscopic Appearance.—1¼ in. of tendon, the distal ¼ in. is marked with surgical clamp and was cut away before blocking. The proximal ½ in. is surrounded with blood clot and/or muscle fibres.

Histology.—Sections have been cut in the long axis of the proximal part of the ruptured tendon, and include a large area of muscular attachment. The site of the rupture is not included since the distal portion of the tendon was not removed and the tendon fibres at the distal end of the excised portion are crushed and torn by the surgical clamp. Pathological changes, however, are extensive in the part which is suitable for histological examination. The collagen fibres of the tendon itself appear normal by both ordinary and polarized light. The bundles show a wavy outline resulting from their slight retraction. Several small blood vessels are seen in the body of the tendon and these are in relation to elongated foci of lymphocytes with occasional polymorph and eosinophil leucocytes intermingled with proliferated endothelial cells and fibroblasts. This chronic inflammatory cellular reaction is much more marked at the edge of the tendon beneath the muscle attachment and between the fibres of voluntary muscle, where there are quite considerable foci of lymphocytes, many fair-sized, thin-walled, blood vessels, and some cellular fibrosis of the endomysium. The synovial covering on either side of tendon and muscle, shows fibroblastic proliferation, great vascularity, and diffuse lymphocytic infiltration with a scattering of eosinophils and polymorphs. Flakes of fibrin deposit are to be seen on one surface. In one or two areas there are small aggregations of histocytes near a vessel wall, between which collagen fibres, showing fibrinoid change, can be identified. Many of the muscle fibres at the extreme distal end of the muscle attachment show waxy degeneration, but with persistence of muscle-cell nuclei beneath the sarcolemma.

The lesion, which is of chronic inflammatory type and can be compared with the lesions of rheumatoid arthritis seen in other sites, may be summarized thus:

(1) rheumatoid tenosynovitis.
(2) rheumatoid myositis with chronic inflammation and lymphocytic infiltration in the endomysium and waxy degeneration of muscle bundles.
(3) vascularization and lymphorrhages in the substance of the tendon.

The whole disturbance can be related to rheumatoid arthritis, and it is probable that this rheumatoid tendinitis has occasioned rupture of the tendon.

Case 3.—A manual worker, aged 58, a heavily-built man, had a history of rheumatic fever in 1930, when he had been treated in hospital for several months, and had made a complete recovery. Since then, he has always worked as a weighing-machine fitter—a skilled, heavy, manual job. He is right-handed. In 1945 he developed pain and swelling of his hands, feet, elbows, and shoulders. A diagnosis of rheumatoid polyarthritis was made at a specialized rheumatism unit, and he received several courses of gold injections in 1947, 1948, and 1949.

In 1949, that is, 4 years after the onset of his rheumatoid arthritis, he was lifting a weight of about 56 lb. with another man, when he felt a sudden tingling in the left thumb and forearm. His grip became weak and he stopped work. Next day, he noticed that his " left thumb had dropped ". At that time his left hand was clinically little affected by the rheumatoid process, and he himself considered it to be his " best hand ".

He was seen at a rheumatism clinic six months later, complaining of his generalized arthritis. Both wrists were thickened and swollen. The erythrocyte sedimentation rate was 48 mm. (Wintrobe), and the condition was active. The spontaneous rupture of the extensor pollicis longus was noted, and repair suggested. This the patient refused, as he

* I am indebted to Dr. D. H. Collins for this report.

considered the disability to be slight, and it did not interfere with his work. *X* ray showed some osteo-porosis of the carpal bones.

When seen two years later, in 1951, at the National Hospital for Rheumatic Diseases, Bath, he had an active polyarthritis of the rheumatoid type, involving hands, wrists, elbows, shoulders, and feet. He was Stage III, Class III, by the Steinbrocker classification. He had soft, crepitant swellings about both wrists, and nodules at both elbows. His hands were soft and loose with little deformity of the proximal interphalangeal joints, but thickening of the metacarpophalangeal joints of both hands. There was obvious wasting of all interossei, and a little thenar loss of tone. There was loss of active extension of the terminal phalanx of the left thumb, and the tendon of the extensor pollicis longus was not palpable at the wrist. The erythrocyte sedimentation rate was 39 mm. (Wintrobe), and radiographs of the wrist showed no change from those taken 2 years earlier. He had no complaints of the function of his left hand, other than a general weakness of grip.

Case 4.—A bus-driver, aged 56, had a generalized rheumatoid arthritis of 10 years' duration. He had deep *x* ray to his wrists and knees in 1949, and in August, 1950, a course of insulin hypoglycaemia, with slight improvement. In February, 1951, whilst washing, he developed pain and swelling of the left wrist, there being no injury of any kind. When seen a week later at the National Hospital for Rheumatic Diseases, Bath, he was found to have a spontaneous rupture of the left extensor pollicis longus. Clinically the disease was moderately active, with involvement of the knees, ankles, and wrists. The erythrocyte sedimentation rate was 66 mm. in the first hour (Westergren). He was right-handed.

Operation was suggested, but the patient was able to carry on with his work, and therefore refused it.

Case 5.—A dentist's wife, aged 51, who had been suffering from a generalized rheumatoid arthritis for 4 years, suddenly felt something "go snap" in the left wrist. Her rheumatoid condition was active at the time, the erythrocyte sedimentation rate being 50 mm. (Wintrobe). She was seen by Dr. G. D. Kersley, and a spontaneous rupture of the extensor pollicis longus was diagnosed. A fortnight later the wrist and forearm were explored; the tendon was found ruptured, and was repaired by transplantation of the extensor indicus proprius into the distal part of the ruptured tendon. A good functional result was obtained.

The findings are summarized in the following Table, to which the cases of von Stapelmohr and Wadstein have been appended.

TABLE
CASES OF RUPTURE OF EXTENSOR POLLICIS LONGUS

Case No.	Sex	Age	Duration (yrs.)	E.S.R. (mm.)	Hand	Operative Repair	Function	Rheumatic Fever
1	M	43	5	20	Both	—	v. good	—
2	M	45	1½	46	L	+	v. good	+
3	M	56	4	48	L	—	good	+
4	M	56	10	66	L	—	v. good	—
5	F	51	4	50	L	+	good	—
Stapel-mohr	M	25	17	—	R	+	good	+
Wadstein	M	32	2/12	18	L	+	excellent	—

Discussion

In view of the histological findings in Case 2, there seems little doubt that spontaneous rupture of the tendon of extensor pollicis longus can occur as a result of the rheumatic disease process. This is strongly supported by the bilateral lesion in Case 1. All five cases reported are closely similar. In each a rheumatoid arthritis of moderate severity was present in a relatively young subject, and the rupture occurred during normal everyday activity without obvious predisposing trauma. Several features seem worth discussing in detail.

Sex.—The sex incidence is possibly significant. Four of the five cases occurred in male subjects, whereas two-thirds of the 148 patients reported by von Stapelmohr were women. In addition, rheumatoid arthritis is more frequent in women than men. Kersley (1950) gives the figures of five women to one man. In this series, the ratio of women to men was approximately 2·4 : 1 (306 : 127). If the two cases of von Stapelmohr and Wadstein are added to the series, the sex incidence becomes even more decisive, as both their cases were males.

Occupation.—The type of occupation may be of some importance. Case 1 was a civil servant, doing clerical work, but his first rupture developed whilst digging. Case 2 was a weaver, doing work involving considerable manual skill, and had been a hospital in-patient for 2 months before his rupture. Case 3 was a machine fitter, doing work that involved both skilled movements and heavy manual labour, and his rupture took place during heavy lifting. Case 4 was a bus-driver, whose hands were thus in constant use. Case 5 did light household duties. The heavier type of work done by men may be the cause of the preponderance of the lesion in men. All the subjects were right-handed, yet the rupture was left-sided in four cases, and bilateral in one. It is difficult to suggest any explanation for this.

Age.—The age range of the five cases was very small, lying between 43 and 56. The cases of Wadstein and von Stapelmohr were rather younger.

Activity of Disease.—All cases were in an active stage of the disease at the time of the rupture, both clinically, and as shown by the erythrocyte sedimentation rate, which varied between 20 and 66 mm. in the first hour.

Duration of Disease.—This varied between 1½ and 10 years before the rupture.

Rheumatic Fever.—Two of the five cases (2 and 3) had histories of rheumatic fever during young adult life. Von Stapelmohr's case also had a " polyarthritis following a carditis " when a child—probably a rheumatic fever.

The exact frequency of rheumatoid arthritis following rheumatic fever is uncertain. The most recent work on the correlation of the two conditions is that of Bywaters (1950), who analysed the literature and a personal series of cases of rheumatic heart disease in rheumatoid arthritis. Of a total number of 241 cases of rheumatoid arthritis described in several series since 1943, autopsy evidence of rheumatic heart disease was found in 34 per cent. Bywaters' own figures of 18 per cent. were reduced to 7 per cent. if the Jaccoud type of chronic fibrous rheumatism following rheumatic fever was excluded. Of a total number of 420 cases of rheumatoid arthritis described in several series since 1943, clinical evidence of

rheumatic heart disease was found in 5 per cent. Though these figures gave no real indication of the number of cases of rheumatoid arthritis with a previous history of rheumatic fever, they suggest that the clinical association of the two (as opposed to autopsy evidence) is uncommon.

The evidence of a previous history of rheumatic fever in this series is much higher (2 : 5) than might be expected, and it may be significant, although the numbers are too small to be of statistical value. In the cases examined in this series, no confirmatory evidence of the history of rheumatic fever was obtained. There was no clinical evidence at the time. No electro-cardiographs were made, but these may well be worth doing on any further cases seen. Although tendons are involved in rheumatic fever (Bywaters, 1950, considers tendon crepitus to be a feature), tendon ruptures have not been described in this disease.

Treatment and Function.—Function was good in all cases, with or without operative repair, and this is probably a reason for the relative infrequence of the diagnosis of the lesion. Deformities of the hand and muscle weakness are accepted by the patient as a feature of the disease. Cases 1, 3 and 4 were diagnosed during routine examination, without any particular complaint by the patient, because the cases were seen by clinicians interested in muscle and tendon lesions in rheumatoid arthritis. (The author had previously seen one of the cases of muscle rupture described by Kersley in 1948.)

Frequency.—The lesion is uncommon. As previously pointed out, the patient may not complain of the loss of thumb extension, and function is usually little impaired. Case 1 did not even complain of bilateral loss; it was found during an investigation of wasting of the muscles of the hands in rheumatoid arthritis, during which 125 cases attending the Rheumatism Out-Patient Clinic at Leeds General Infirmary in 1949 were studied. In no other subjects were tendon ruptures found. During the same period, eighty cases of rheumatoid arthritis were similarly investigated at the Royal Bath Hospital, Harrogate, and tendon rupture was found only in Case 2. This gives a total of two out of 205 cases. The next year, 228 cases of rheumatoid arthritis were examined in detail at the Rheumatism Clinic of the Royal Free Hospital, London, and no tendon ruptures were found. This brings the figure for the number of ruptures found on detailed, but routine, clinical examination to two out of 433 cases (approx. 0·5 per cent.).

Summary

(1) The literature on spontaneous rupture of the tendon of the extensor pollicis longus is reviewed, and the occurrence of tendon lesions and spontaneous muscle ruptures in rheumatoid arthritis is noted. Only two cases could be found in the literature in which rheumatoid polyarthritis was considered to be the causative factor.

(2) A series of five cases (one bilateral) occurring as a complication of rheumatoid arthritis are described, and the relative frequency, sex incidence, and other possible aetiological factors of the tendon rupture are discussed.

I am indebted to Dr. G. D. Kersley of the Rheumatism Research Unit, Bath, for permission to use his Cases 3, 4, and 5, to Dr. L. Mandel for kindly providing the histories of Cases 4 and 5, to Dr. D. H. Collins for his pathological report on Case 2, to Mr. H. Petty for operating on Case 2, to Professor S. J. Hartfall for permission to use his cases at Harrogate and Leeds, and to Dr. E. Fletcher for permission to use his cases at the Royal Free Hospital, London. I also wish to thank Dr. E. Fletcher and Dr. G. D. Kersley for their advice and encouragement.

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Rupture Spontanée du Tendon du Long Extenseur du Pouce comme Complication de l'Arthrite Rhumatismale

Résumé

(1) On passe en revue la littérature sur la rupture spontanée du tendon du long extenseur du pouce et on enregistre l'apparition de lésions tendineuses et de ruptures spontanées des muscles au cours de l'arthrite rhumatismale. On n'a trouvé dans la littérature que deux cas où la polyarthrite rhumatismale a été considérée comme facteur causatif.

(2) On décrit cinq cas (dont un bilatéral) de complication de ce genre dans l'arthrite rhumatismale et on discute la fréquence relative, l'incidence selon le sexe, et d'autres facteurs étiologiques possibles de la rupture tendineuse.

Ruptura Espontánea del Tendón del Extensor Largo del Pulgar como Complicación de la Artritis Reumatoide

Sumario

(1) Se pasa en revista la literatura relativa a la ruptura espontánea del tendón del extensor largo del pulgar y se nota que lesiones tendinosas y rupturas espontáneas de los músculos suelen producirse en casos de artritis reumatoide. En la literatura se encontró solamente dos casos en los cuales la poliartritis reumatoide fué considerada el factor causante.

(2) Se describe cinco casos (uno bilateral) de complicación de este tipo de la artritis reumatoide y se discute la frecuencia relativa, la incidencia según el sexo, y otros factores etiológicos posibles en la ruptura tendinosa.

MONARTICULAR TRAUMA AND RHEUMATOID ARTHRITIS

BY

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It is believed that trauma may precipitate a first attack of rheumatic fever, and it is obviously true that local trauma may give rise to chronic monarticular arthritis. Chronic polyarthritis is another matter, since it is a systemic disease; yet Smith (1932) analysed the histories of 96 patients with rheumatoid arthritis and found that six were precipitated by injuries, which in five cases were monarticular sprains. Pickard (1947) reported that seven out of 35 cases of rheumatoid arthritis in children had been precipitated by injury to a joint; in a series reported by Bille (1948) the proportion was three out of 65 children. Finney and others (1947) reported that monarticular trauma had precipitated an initial attack or a relapse in five out of 100 cases in the U.S. Army.

The work of a number of European writers, who have discussed this subject during the past 20 years, has been reviewed by Jonsson and Berglund (1949). Edström (1942) reported five cases of rheumatoid arthritis in which monarticular trauma seemed to be the sole precipitating factor, and accepted the view of Klinge (1934) that the polyarthritis is an allergic reaction to tissue damage.

Rydén (1943) analysed the histories of 900 cases, and in nineteen found that rheumatoid arthritis had been precipitated by injury to a joint, and had extended to other joints in less than 6 months. He believed that septic teeth or tonsils were partially responsible for the disease in fifteen cases; he concluded that trauma may affect anyone whose mesenchymal tissues are susceptible, through infection or other constitutional factors, to a hyperergic reaction, and that this condition of susceptibility may fluctuate in an individual patient and vary from patient to patient.

Jonsson and Berglund (1949) did not consider trauma as a cause of rheumatoid arthritis if the following six conditions had not been fulfilled:

(*i*) No previous history of rheumatoid arthritis.
(*ii*) Injury to previously healthy joint.
(*iii*) Joint painful or swollen soon after the injury.
(*iv*) No decrease in pain and swelling before involvement of other joints.
(*v*) Spread to other joints not too long delayed.
(*vi*) Certain diagnosis of rheumatoid arthritis.

Of 1,669 cases of rheumatoid arthritis reviewed, Jonsson and Berglund found in twelve that the first sign of rheumatoid arthritis had been precipitated by injury to a joint, and that other joints had been involved within the year. In seven of

these cases, however, one or more of the conditions was not fulfilled, and in four the authors found evidence of infection which (they thought) explained the arthritis. Thus only one case remained, which they did not consider sufficient evidence to establish trauma as a possible cause.

Jonsson and Berglund submitted the traumatic aetiology of rheumatoid arthritis to a rigid and exclusive test, demanding unbroken continuity of symptoms, both in the injured joint and in the spread of the process to other joints, in a patient who has never had arthritis before. It is hardly logical, therefore, to dismiss the evidence when the result of the test is positive. The exclusive role of trauma having been proved in that one case, it must be allowed as at least an important factor in all twelve cases. Other relevant articles are listed in the Additional Bibliography and in Table I.

Present Series of Cases

That injury precipitates chronic polyarthritis, is amply confirmed by my own experience (Kelly, 1948, 1949, 1951). In more than fifty patients out of 600 personally observed, injury was the sole visible factor; but this study is confined to 32 patients in whom the first symptoms appeared immediately after an injury to a single joint not previously injured before. The joint remained painful and swollen, for periods varying from one week to two years, until a second joint was involved, and in most cases a number of joints were then affected in a short time.

Table II (pp. 310 to 315) shows the 32 cases in order of authenticity. Cases 1 to 11 are so recent and so well documented that there is no doubt about the continuity of symptoms. In Cases 12, 13, 14, there was a gap of a few days between the infliction of the injury and the appearance of arthritis. The possibility of error increases in Cases 15 to 32, as the histories reach back into the past. In each case, however, the patient cannot be shaken from a clear story of injury followed by polyarthritis without a break in the symptoms.

Possible complicating factors occur as follows:

(*i*) Multiple injuries (Cases 9, 10).
(*ii*) Possibility of infection through wounds (Cases 10, 11, 24).
(*iii*) Additional damage to same joint (Cases 16, 18, 22).
(*iv*) Ulnar nerve lesions (Cases 15, 29).
(*v*) Constitutional predisposition. No. 13 had iritis in 1940, and his mother suffers from rheumatoid arthritis. No. 16 had had an intractable attack of sciatica in 1920, and his mother had suffered from severe rheumatoid arthritis.

In Cases 19, 22, and 28, it could be objected that the spread to other joints was too long delayed, and in Case 28 that the joints involved are too few. In Cases 7 and 8 the period of observation was perhaps too short; so that we do not know what other factors might have appeared by this time. In Cases 6 and 30 (injuries to the back) more than one joint could have been injured.

But these are not valid objections. Not one of them argues against the influence of trauma; rather do they help to explain it. The aetiology of rheumatism is multiple, and a synchronization of precipitating and predisposing factors is often required to set the unknown mechanism in motion, though sometimes a single injury to a single joint acts as the " trigger ".

Traumatic Rheumatoid Arthritis

Thus we have a variety of rheumatism that may be called " traumatic rheumatoid arthritis "; its incidence as reported by previous workers and in the present series is shown in Table I. This type of rheumatic disease offers special opportunities for study, because it provides us with a human experiment, in which the disease

TABLE I

INCIDENCE OF TRAUMATIC RHEUMATOID ARTHRITIS

Author and Date	Cases of Rheumatoid Arthritis		No. Caused by Trauma
	No.	Remarks	
Bille (1948)	65	Children treated with gold	3
Cecil and Kammerer (1951) ..	100	Aged patients	5
Copeman (1936)	12	Pulmonary T.B. suspected	2
Davison and others (1950) ..	13	Cases treated with pregnenolone	1
Edström (1942)	262	Unselected	5
Finney and others (1947) ..	100	Soldiers	5
Garrod (1888)	100	Unselected	3
Jonsson and Berglund (1949) ..	1,669	Unselected	12
Kuhns (1945)	3	Monarticular onset	1
Lockie and Norcross (1948) ..	28	Children	3
Myers (1951)	10	Cases treated with pregnenolone	1
Nissen and Spencer (1934) ..	4	Patients who died	1
Pickard (1947)	35	Children	7
Ropes and Bauer (1945)	11	Cases of atypical onset	1
Rydén (1943)	900	Workers' compensation cases	19
Smith (1932)	96	Unselected	5
Present Series	600	Unselected	32
Total	3,908		106

begins in a certain joint in response to a known stimulus, and spreads in a regular manner to other joints. It remains now to discover if traumatic rheumatoid arthritis differs in any way from the ordinary clinical picture.

Age.—The average age at onset is 40, a little younger than that of the general run of patients; in 568 non-traumatic cases the mean age at onset was 42·5 years. In Rydén's series the mean age was 36 years, his patients being nearly all men who had been injured at work.

Sex.—In the larger series, the women outnumbered the men by two to one; but sixteen of the 32 traumatic cases were male—doubtless because men are exposed to trauma more than women. Sixteen of Rydén's nineteen industrial cases were men.

Clinical Picture.—From patient to patient, rheumatoid arthritis shows every possible

TABL

ANALYSIS OF 32 CASES OF TRAU

Case No.	Sex and Age (yrs)	Injury			Latent Period	Spr
		Joint	Date	Nature		Order
1	M 29	R. knee	Oct., 1949	Severe blow	4/52	L. knee, L. shoulder, back, feet
2	F 18	L. knee	Jan., 1948	Sprain while dancing	2/52	R. knee, wrists, hips
3	F 28	L. wrist	1945	Sprain	4/12	Shoulders, knees, elbows, feet
4	F 71	R. knee	Oct., 1946	Fall	5/12	L. knee, hands, wrists
5	F 60	L. knee	Apr., 1947	Severe sprain; 1/52 bed	2/52	Wrists, ankles
6	F 31	Lumbar spine	Oct., 1949	Heavy fall; tripped	2/12	Hands, wrists, knees, shoulders, feet, ankles, hips
7	M 31	L. knee	Apr., 1943	Blow	2/12	R. knee, hands
8	M 55	R. ankle	1941	Severe sprain	8/52	L. ankle, R. hand, wrists, L. elbow, R. shoulder
9	M 36	L. thumb (base)	July, 1949	Fracture: slow union; 10-ft. fall; contusions	3/12	Knees, back, ankles, feet, wrists, elbows
10	M 31	R. knee	Oct., 1947	Leg crushed; abrasion	6/52	L. knee, feet shoulders
11	M 37	R. foot	Nov., 1948	Severe blow; abrasion	1/52	All joints
12	M 40	R. wrist	Oct., 1948	Fall -	3/12	L. knee, R. knee
13	M 27	L. knee	Sept., 1947	Fall down stairs	4/52	R. ankle, R. knee, back, hips, wrists
14	F 49	L. elbow	Sept., 1948	Painful blow	5/12	R. shoulder, L. shoulder

E II
MATIC RHEUMATOID ARTHRITIS

ead	Involvement of Joints				Later History	Remarks
Rate	Number	Size	Intensity	Duration		
Rapid	Few	Large	Severe	Transient	Remission in 9/12	Wasted quadriceps
Rapid	Few	Large	Severe	Persistent	Bedridden with ankylosed hips	
Medium (6/12)	Several	Large	Mild	Intermittent	R. knee persistently painful	Army nurse
Rapid	Several	Large	Severe	Persistent	Severe deformities of knees and wrists	
Medium (5/12)	Few	Small	Mild	Transient	History after Dec., 1947, unknown	
Rapid	Many	Both	Severe	Persistent		Still works as a nurse
Rapid	Few	Both	Mild	Peri-articular	History after Aug., 1943, unknown (Army)	
Rapid	Several	Large	Moderate	Intermittent	History after 1942 unknown	
Rapid	Many	Large	Severe	Transient	Remission in 10/12. Persistent backache	
Rapid	Several	Large	Moderate	Persistent	Painful deformity of shoulders, feet	
Very rapid (3 days)	Many	All kinds	Acute	Transient	Persistent disability of shoulders	
Slow (9/12)	Few	Large	Hydrarthrosis	Persistent	History since Sept., 1949, unknown	
Medium	Many	Large	Severe	Persistent	Poker back, kyphosis, lost 70 lb.	Constitutional
Slow (2/12)	Shoulders	only	Severe	Subsiding	Slight stiffness of shoulders	

TABLE

Case No.	Sex and Age (yrs)	Injury			Latent Period	
		Joint	Date	Nature		Order
15	M 65	R. elbow	1946	Fall; ulnar lesion	2/52	Hands, feet, knees, shoulders
16	F 55	R. knee	1947	Fall; synovitis; manipulated at 3/12	3/12	Hands, shoulders, most joints
17	M 45	R. elbow	1945	Fracture	6/62	L. elbow, knees, back, feet, fingers
18	F 51	R. knee	1934	Fall; synovitis; manipulated at 2/12	2/12	Back, shoulders, R. knee
19	M 15	R. knee	1947	Sprain: synovitis	2 yrs	Ankles, R. hip, feet
20	F 44	R. thumb	1945	Twisted in play	3/52	L. thumb, wrists, fingers
21	F 59	R. knee	1940	Ran for train; synovitis	6/12	Shoulders, neck, L. knee fingers
22	M 27	L. wrist	1936	Scaphoid; non-union; drilled three times	2 yrs	R. wrist, L. elbow, hands, knees, ankles
23	F 31	L. foot	1934	Severe sprain; 3/52 bed	3/12	R. hand, most joints
24	M 42	L. index	1934	Knock; abrasion	1/52	L. wrist, R. elbow, L. elbow, fee
25	F 45	R. knee	1934	Fall	5/12	L. knee, back, feet, fingers
26	F 36	R. toe	1936	Stubbed toe	3/52	Hands, shoulders
27	M 60	R. wrist	1934	Heavy fall; swelling five days later	3/52	L. wrist, L. shoulder, R. shoulder, many joints

continued

ead	Involvement of Joints				Later History	Remarks
Rate	Number	Size	Intensity	Duration		
Rapid	Many	Both	Severe	Subsiding	Painful L. shoulder, deformities of hands and feet	
Rapid	Many	Both	Severe	Subsiding	Flexion deformity of knee	Constitutional
Rapid	Many	Both	Severe	Subsiding	Remission in four years	
Rapid	Several	Both	Moderate	Intermittent	Residual pains in hands, wrists, feet	
Slow	Few	Large	Severe	Persistent	Persistent hydrarthrosis of knee, other joints mild	
Rapid	Few	Small	Moderate	Transient	Remission 18/12. Relapse 1948; many joints	
Slow	Few	Both	Severe	Subsiding	Residual deformities of R. knee and three fingers	
Rapid	Many	Both	Severe	Persistent	Gradually subsided in 12 years	
Slow	Many	Both	Moderate	Intermittent	Residual deformities of wrists, fingers, feet	
Rapid	Many	Large	Severe	Resolving	Painful swelling of elbows, other joints fair	
Medium	Many	Both	Severe	Slowly resolving	Pain in R. knee only. Residual deformity of fingers	
Rapid	Few	Small	Moderate	Transient	Remission in 18/12. Transient pains 10 yrs. Relapse 1948, many joints	
Rapid	Many	Both	Severe	Persistent	Pain and stiffness in many joints. No acute inflammation.	

TABLE I

Case No.	Sex and Age (yrs)	Injury			Latent Period	S
		Joint	Date	Nature		Order
28	M 43	L. ankle	1937	Severe sprain	2 yrs	R. ankle, feet, backache
29	F 33	R. elbow	1933	Fall; ulnar lesion	2/12	R. hand, shoulders, L. hand, feet
30	F 28	Lumbar spine	1935	Fall from horse	10/12	Wrists, fingers R. shoulder, R. foot
31	M 8	L. knee	1908	Fall	8/12	L. foot, R. knee, R. foot, hip
32	F 2½	L. knee	1925	Pushed; fall	6/12	R. knee, hips, back, etc.

variation in rate of spread, intensity of inflammation, and number of joints involved. This variability renders difficult the comparison of a small series with one seventeen times larger; but the traumatic cases are not perceptibly more or less severe than the others, either in intensity of inflammation or in the number of joints involved (see Columns 6 to 10, Table II).

Order of Joint Involvement: Symmetry.—More than half of the total cases of rheumatoid arthritis were symmetrical from the beginning and chiefly involved small joints. This was also the experience of Short and Bauer (1948) and Egelius and others (1949). In those caused by monarticular trauma, however, the disease must be asymmetrical at the beginning, and large joints are usually involved (Table III), but in most cases it becomes symmetrical early in its course.

In thirteen out of thirty unilateral cases—excluding the two spinal injuries—the second joint involved was the opposite fellow of the injured one, and in twelve

TABLE III
INJURED JOINT IN TRAUMATIC RHEUMATOID ARTHRITIS

Joint	Present Series	Other Cases*
Knee	14	14
Wrist	4	7
Elbow	4	1
Foot	3	2
Hand	3	1
Ankle	2	10
Back	2	0
Shoulder	0	1
Total	32	36

* In many recorded cases this detail has not been supplied.

ntinued

ad	Involvement of Joints				Later History	Remarks
Rate	Number	Size	Intensity	Duration		
ery slow	Few	Large	Severe	Persistent	Ankles still painful and swollen	
low	Few	Small	Moderate	Persistent	Nodules on deformed finger-joints	
low	Few	Large	Severe	Persistent	Activity in L. wrist and R. shoulder, ankylosis of R. wrist	
apid	Many	Large	Severe	Ankylosing	Hips, spine, and many other joints ankylosed	
apid	Many	Large	Severe	Ankylosing	Hips, spine, and many other joints ankylosed	

the second appearance of rheumatic disease was the simultaneous involvement of symmetrical joints (both hands, both wrists, etc.).

A normal joint recovers from traumatic synovitis. In the establishing of polyarthritis after trauma, therefore, there are two unusual features:

(*i*) failure of injured joint to recover,
(*ii*) spread of effects to other joints.

Failure of Injured Joint to Recover.—This is the result of the interaction of two factors:

(*i*) overuse of injured joint;
(*ii*) disturbed joint physiology.

Over-use of Joint.—Rydén found that fourteen of his nineteen patients caused further damage by continuing at work with the joint painful and swollen, or by returning to work before complete recovery.

In Case 10 of the present series the knee, though painful, did not swell until the patient tried to work a month after the injury. In Cases 2, 3, 4, 6, 8, 12, 13, and several others, normal activity was pursued after the injury. Physiological use of a painful and swollen joint imposes a strain on it, and any movement of inflamed synovial tissues amounts to trauma. Thus a vicious circle might set in; but most injured joints recover even when used a good deal, and another factor is required to maintain the diseased state.

Disturbed Joint Physiology.—Bennett (1943) pointed out that the persistence of hydrarthrosis after trauma indicates that the joint physiology has been fundamentally disturbed. In the hypersecretion of fluid, disordered reflexes play a large part (Leriche, 1928; Pétrignani, 1932).

Spread of Effects to Other Joints.—Rydén believed that occupational strain of the damaged joint, combined with a constitutional factor (bacterial allergy), was responsible for the general spread. And indeed there is evidence that further articular damage plays a part. The general spread took place in Cases 16 and 18

immediately after the knee joints had been manipulated for " slipped cartilage ", and in Case 22 after the scaphoid bone had been drilled for non-union. In a patient reported by Ropes and Bauer (1945), the ankle and the opposite knee swelled after a semi-lunar cartilage had been removed at operation.

The Constitutional Factors.—Of these we have no knowledge in this disease, apart from

(*i*) the undoubted predisposing influence of heredity (see Cases 13, 16),
(*ii*) the astonishing effect of cortical hormones—which are not themselves deficient in the body (Hench and others, 1950).

To say, " he has the disease, therefore he must have been predisposed ", is not valid reasoning; such a *non sequitur* could be applied to cancer, tuberculosis, or almost any other disease; each malady has been called constitutional while its cause was unknown. According to Hunter (1835):

> Perhaps there is no term so vague or so undetermined in the mind as the term constitutional. Universal action of every kind may be called constitutional, even when arising from some local cause.

Eight of the 32 patients were over 50 years of age before the occurrence of the accident which brought on the disease. Case 4 had lived for 71 years without rheumatism, but after an injury her knee remained painful and swollen for 5 months before the second knee became involved; then the spread was more rapid. This history does not suggest a permanent constitutional defect, awaiting its opportunity to strike, but that the factor which favoured the spread of the disease was not present until 5 months after the injury.

This factor is probably a late change in the organism; an induced, and possibly transient, state of receptiveness which allows the disorder to spread and become firmly established. If the disease were truly allergic we should expect the joints to be picked out in irregular fashion; but on inquiry we find that it has a remarkable preference for the symmetrically opposite joint (see Table IV). For the same reason, it cannot be due to any material (neoplastic, infective, or chemical) carried by the blood or the lymph stream.

TABLE IV
SYMMETRICAL SPREAD OF TRAUMATIC RHEUMATOID ARTHRITIS

Author and Date	No. of Cases in which Details were Given	No. in which First Spread was Symmetrical
Copeman (1936)	2	0
Davison and others (1950) ..	1	0
Edström (1942)	4	4
Jonsson and Berglund (1949) ..	1	0
Kuhns (1945)	1	0
Myers (1951)	1	0
Nissen and Spencer (1934) ..	1	1
Pickard (1947)	1	1
Ropes and Bauer (1945)	1	0
Rydén (1943)	19	6
Present Series	30*	13
Total	62	25

* In two cases the back (a mid-line structure) was injured.

In the precipitation of rheumatoid arthritis by damage to a joint, there is no analogy with the lighting up of septicaemia by injury. Organisms gain a foothold in the damaged tissues, and later spread by the blood stream, resistance to the spread of infection depending on serological developments. In polyarthritis no one now believes that organisms are present in the joints or that its spread is resisted by antibodies in the serum.

The Neural Factor.—If the spread were entirely fortuitous, it would be symmetrical in perhaps three cases out of the thirty, instead of in thirteen. (Other writers have recorded the same preference for the opposite joint, see Table IV.) And in twelve of the remaining nineteen cases the first spread was to two symmetrical joints. Since symmetry in a disease can suggest only the involvement of nervous channels, it appears that the constitutional factor in traumatic rheumatoid arthritis involves a disturbance of the central nervous system.

Paget (1879), who wondered about the symmetry of many rheumatic lesions, postulated at first an exact similarity of chemical composition which rendered symmetrical structures equally attractive to circulating toxins. But he changed his opinion when he saw that the appearance of the lesions on the second side was often delayed for months or years. He wrote:

> It is clearly probable that the symmetrical distribution of diseases on corresponding portions of the extremities should depend on central nervous connections rather than on any assumed identity of chemical composition.

In a previous series of articles (Kelly, 1945, 1946a, b), I presented a neural theory of rheumatic disease. This was not a new theory but a very old one which had been held by all the great clinicians of the 19th century (Garrod, 1888); it had never been disproved, but had been abandoned when everyone became convinced that the new science of bacteriology was about to solve every problem. Evidence in favour of the neural theory continues to accumulate; relevant articles are listed in the Additional Bibliography, and I can only repeat my previous conclusion:

> The verification of this hypothesis depends upon the painstaking and careful observation of mild and transient cases of somatic pain, and of early cases of rheumatic disease.

Traumatic rheumatoid arthritis, which gives us an opportunity of observing the early spread of the disease from a single lesion, may also contribute in striking fashion to the verification of the neural hypothesis.

Summary

(1) In 32 cases of rheumatoid arthritis, in which the only visible causative factor was injury to a single joint, the clinical picture of the established disease did not differ perceptibly from the usual.

(2) Before spreading to other joints, the disease was monarticular for periods up to two years. It went first to the opposite joint in thirteen cases, and simultaneously to two symmetrical joints in twelve.

(3) The persistence of chronic arthritis in an injured joint depends on two factors:

(*i*) further damage to the joint by overstrain;

(*ii*) reflex disturbance of joint physiology.

(4) The commencement of spread frequently followed overstrain or further damage to the injured joint; symmetry suggests that the change is propagated through nervous channels.

(5) It is concluded that the constitutional factor which favours the spread of the disease is not a permanent defect but a late disturbance of the nervous system, induced by impulses from the damaged tissues.

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Traumatisme Monoarticulaire et Arthrite Rhumatismale

RÉSUMÉ

(1) Dans 32 cas d'arthrite rhumatismale, dans lesquels le seul facteur causatif visible était un traumatisme d'une seule articulation, le tableau clinique de la maladie à la période d'état ne sortait pas sensiblement de l'ordinaire.

(2) Avant de s'étendre aux autres articulations, toutefois, la maladie demeurait monoarticulaire pendant des périodes allant jusqu'à deux ans. Dans 13 cas elle passa d'abord à l'articulation du coté opposé et, dans 12 cas, simultanément, à deux articulations symétriques.

(3) La persistance de l'arthrite chronique dans une articulation lésée dépend de deux facteurs:

(*i*) altération subséquente de l'articulation par surmenage;
(*ii*) troubles réflexes de la physiologie articulaire.

(4) Le début de l'extension suivait souvent le surmenage ou des lésions ultérieures de l'articulation qui avait subi le traumatisme; l'existence de la symétrie fait penser à la propagation des altérations par des voies nerveuses.

(5) On conclut que le facteur constitutionnel qui favorise l'extension de la maladie n'est pas un défaut permanent mais un dérangement tardif du système nerveux, provenant de la stimulation originant des tissus endommagés.

Traumatismo Monoarticular y la Artritis Reumatoide

SUMARIO

(1) En 32 casos de artritis reumatoide, en los cuales el único factor causante visible fué un traumatismo en una sola articulación, el cuadro clínico de la enfermedad establecida no se distinguía perceptiblemente de la forma usual.

(2) Antes de extenderse a otras articulaciones, sin embargo, la enfermedad se mantuvo monoarticular hasta por dos años. Atacó primeramente la articulación opuesta en trece casos y, simultáneamente, a dos articulaciones simétricas, en doce.

(3) La persistencia de artritis crónica en una articulación traumatizada depende de dos factores:

(*i*) daño subsiguiente por fatiga excesiva de la articulación;
(*ii*) disturbios reflejos de la fisiología articular.

(4) La extensión del mal solía iniciarse después de la fatiga excesiva o de daño subsiguiente causado a la articulación afectada; la existencia de la simetría sugiere que los cambios mórbidos se propagan a través de las vías nerviosas.

(5) Se concluye que el factor constitucional que favorece la extensión de la enfermedad no es un defecto permanente sino un disturbio tardío del sistema nervioso, inducido por impulsos procedentes de los tejidos dañados.

SPLENECTOMY IN RHEUMATOID ARTHRITIS*

BY

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Chevallier (1930) emphasized the similarity of the Chauffard-Still's disease to the " rhumatisme bilaire " described by Gilbert and by Fournier, and to the arthritic manifestations of the " cirrhoses bilaires " mentioned by Hanot. After describing the ineffectiveness of various forms of medical treatment, he noted that, as far as he knew, in no instance had the spleen been removed, although it was known that in patients with splenic enlargement the associated symptoms often abated after removal of the spleen, and commented that splenectomy might be worth trying. Hanrahan and Miller (1932), and Craven (1934), reported the result of splenectomy in Felty's syndrome in two women aged 50 and 40 respectively. After the operation a clinical improvement was noted with reduction of pain and joint stiffness. Fitz (1935), however, in a discussion on Felty's syndrome, stated that both these patients had died within 18 months of the operation. Loeper, Lemaire, and Patel (1937) reported the successful removal of the spleen in a woman aged 28 who was suffering from advanced rheumatoid arthritis; but 35 days after the operation she developed pneumonia and died. Pointing out that in this disease there is a diffuse mesenchymal reaction characteristic of an infective disease, they suggested that it might be looked on as one of the " reticulo-endothelioses " and that although the aetiology might be unknown, this would give a reason for the clinical improvement following splenectomy.

In 1938, at my instigation, the spleen was removed in three patients under my care at St. Stephen's Hospital, who were suffering from rheumatoid arthritis in an active and advanced stage. In reporting this, we stated (Bach and Savage, 1940) that we did not know the aetiology of rheumatoid arthritis, and were not prepared to estimate the role of the spleen in this disease. As the clinical improvement following splenectomy impressed me, two more patients in the unit were subjected to this operation in 1944-45, and two or three elsewhere, of whom I have no further record. I then stopped this somewhat drastic treatment until after my return from the United States in 1949. The work of Hench and Thorn had now given us much to think about, though I was not convinced that cortisone was the final answer, nor that the adrenal cortex was the only " villain of the piece ". I reviewed my splenectomy patients, and seeing that they had not done too badly,

* Read at a meeting of the Heberden Society on December 8, 1950.

asked my surgical colleagues to try again. Their results in six cases are summarized below, but before passing to the clinical reports, one or two more articles in the literature deserve attention. Mention was made by McElin and Mussey (1950) of Galen's ancient comment that the spleen was an organ full of mystery, and to the more recent statement by Zondek (1944) that the spleen is an endocrine gland. Barcroft and Stevens (1928) and Barcroft (1930a, b) noted a decrease in the size of the spleen in pregnant dogs, and pointed out that the contraction could be divided into "heat" contraction, "pregnancy" contraction, and "lactation" contraction. Contraction could be abolished by denervation in the first two, but not in the third. This suggested that contraction during heat and pregnancy are neurogenic in origin, but that in lactation there is a large humoral element, and the theory was advanced that the spleen contracted during pregnancy to supply more blood to the genital organs because of the dilatation of the uterine vessels, and to aid in foetal haematopoiesis.

Gottesman and Perla (1930) and Perla (1936) showed that the removal of the hypophysis in the adult rat was followed by progressive atrophy of the spleen, which suggested that the anterior hypophysis secreted a stimulating factor for the spleen. Edwards and Wright (1937) removed the spleen in rats and noted that two weeks later the hypophyses in these rats had become some 25 per cent. larger than those in the control animals. The pituitary showed an increase in the reticulo-endothelial elements and increased mitosis of the basophil cells.

Valid proof of an internal secretion of the spleen did not exist, but Ungar (1945) presented experimental evidence suggesting that the spleen produced, and could release into circulation, a substance which acted like a hormone. This he termed Splenin (Splenin A, which decreases capillary permeability and bleeding time, and Splenin B, which increases capillary permeability and bleeding time). Witts (1948) reported on splenectomy in the "reticuloses", a generic histological term to describe all the progressive hyperplasias of the reticular tissues, which include Hodgkin's disease, certain of the leukaemias, and other forms of non-malignant lymphadenopathy. It was noted that in experimental animals, splenectomy had been followed by moderate anaemia, leukocytosis, and thrombocytosis, together with increase in bone marrow and hyperplasia of lymphoid tissue. In general, removal of the spleen appears to stimulate the mesenchymal reticular cells throughout the body to increased function and differentiation. He pointed out that there is little exact information as to what happens when the normal adult human spleen is removed. There is no significant anaemia, but there is considerable leukocytosis and thrombocytosis. In brief, the spleen appears to exert an inhibitory influence on the bone marrow. When this inhibition is removed the emission of white cells and platelets from the bone marrow is accelerated. Duthie (1950) suggested the possibility that in certain circumstances the spleen secretes a substance which antagonizes the action of the adrenal steroids. A review of the literature does suggest the existence of an interrelationship between spleen and pituitary, spleen and ovaries, spleen and bone marrow, and, finally, between spleen and adrenal cortex.

Clinical Material

First Group.—Three patients whose spleens were removed in 1938.

Case 1.—Woman, aged 29, followed up for 12 years. Seen last summer. Severe long-standing rheumatoid arthritis which has remained relatively inactive for 12 years. She presents three points of interest:

(1) At the present time she is in hospital for an orthopaedic operation to strengthen her deformed knees. The " fire " has burnt out, and she is left with the " ashes " of the disease.

(2) There has been definite radiological evidence of increased destruction of the joints of the hands and wrists.

(3) Twelve years ago at operation amyloid changes were seen in the spleen. The blood sedimentation rate has returned to the upper normal limit.

Case 2.—Girl, aged 18, followed up for 6 years from 1938-1944. The spleen at operation showed amyloid disease. She was later admitted with gastro-enteritis to another hospital, where she died. I saw the *post-mortem* examination. Very few joint changes were noted, but the liver showed amyloid disease.

Case 3.—Boy, aged 18, not traced in spite of repeated efforts.

Second Group.—Two patients whose spleens were removed in 1944 and 1945.

Case 1.—Girl, aged 24, followed up for 6 years from 1944 to 1950. She was under my care at St. Thomas's Hospital for three years prior to operation, and failed to respond to routine methods of treatment. After the operation there was marked relief of pain and stiffness and improvement of her general health, and she has been at work for the past five years. The blood sedimentation rate, before operation, was always around 60 mm. in the first hour, but since the operation it has varied from 10 to 15 mm.

Case 2.—Boy, aged 24, followed up for 5 years from 1945 to 1950. At the age of 24, the onset of acute rheumatoid arthritis followed thyrotoxicosis. Since splenectomy, the disease has been clinically inactive, and the patient has been leading a restricted but full life as a cripple. Again the " fire " has been extinguished, but the " ashes " remain. Prior to operation the blood sedimentation rate was 80 mm., and since, it has remained constant at about 5 mm. It is interesting to consider the possible relationship between thyrotoxicosis, thyroidectomy, and the onset of rheumatoid arthritis.

Third Group.—Six cases operated on in 1949 and 1950. The findings in this last group are set out in the Table, and the pathological reports are summarized below. Two patients were suffering from acute rheumatoid arthritis and four from chronic arthritis. As they had all been under observation for a considerable period, and had failed to respond to other forms of therapy, it was decided to carry out splenectomy to see if this would arrest the progress of the disease. No immediate clinical improvement appeared in the first few months after the operation, but the follow-up 8 to 13 months later showed that one acute case (No. 6) appeared to be quiescent, four cases had improved, and one (No. 1) had had a slight relapse but was better than before the operation.

In all cases the sedimentation rate fell; the red-cell count rose in three cases (Nos 2, 4, 6), and the white-cell count showed a consistent rise in all. The plasma proteins rose in four cases (Nos 1, 2, 3, 4), but fell again in the following months. The alkaline phosphatase rose in the five cases in which it was estimated.

TABLE

PARTICULARS OF SIX CASES IN GROUP THREE

Case No. and Year of Onset	Date of Test	Red Blood Count	Haemoglobin (per cent.)	White Blood Count	Blood Sedimentation Rate	Serum Protein		Thymol Turbidity Test	Colloidal Gold Reaction	Alkaline Phosphatase
						Total	A/G Ratio			
1. 1937	9.1.50	4·96	81	5,100	50	7·8	2·9 : 1	2	Neg.	11·2
	16.1.50					*Splenectomy*				
	13.2.50	4·05	75	10,300	25	8·3	2·5 : 1	2	Neg.	7·5
	19.10.50	3·96	80	10,900	20	—	—	—	—	—
	29.11.50	—	—	—	30	6·3	1·7 : 1	1	Neg.	12·6
2. 1940	11.11.49	4·16	83	6,900	60	6·8	1·7 : 1	6	3+	7·1
	15.11.49					*Splenectomy*				
	12.12.49	4·36	88	12,100	60	7·8	2·8 : 1	5·5	2+	14·6
	17.6.50	—	92	11,600	32	—	—	—	—	—
	23.11.50	5·3	105	10,100	28	6·6	1·7 : 1	—	—	—
3. 1942	11.11.49	4·08	83	9,300	30	7·8	2·3 : 1	4	Neg.	4·7
	15.11.49					*Splenectomy*				
	12.12.49	4·29	88	10,700	20	8·9	2·3 : 1	3	Neg.	6·1
	23.9.50	4·17	78	11,000	12	7·2	1·7 : 1	—	—	—
4. 1946	14.4.49	3·76	75	5,400	40	7·9	1·3 : 1	14	5+	3·6
	18.10.49					*Splenectomy*				
	3.11.49	4·19	85	9,700	50	—	—	13	5+	9·2
	14.11.49	—	—	—	50	10·5	0·9 : 1	—	—	—
	28.4.50	4·15	80	8,500	62	10·3	1·1 : 1	15	5+	8·4
	29.11.50	4·25	80	11,600	28	—	—	12·5	5+	10·1
5. 1949	20.7.49	3·8	58	17,600	46	—	—	—	—	—
	22.9.50	4·5	76	20,000	60	6·0	0·7 : 1	—	—	—
						Splenectomy				
	4.11.50	4·07	77	18,500	42	—	—	—	—	—
	16.11.50	4·08	82	18,000	27	5·7	1·5 : 1	—	—	—
6. 1949	6.1.50	3·88	77	12,100	50	—	—	—	—	—
	22.2.50	3·74	70	10,000	98	9·3	1·5 : 1	13	2+	4·2
	11.4.50					*Splenectomy*				
	3.5.50	2·66	53	11,650	100	8·9	2·2 : 1	5	2+	6
	7.6.50	3·61	84	—	90	—	—	—	—	—
	27.10.50	5·62	110	8,500	5	7·0	1·3 : 1	3	Neg.	11·2

Case 6 is of unusual interest. This patient was first admitted to the Middlesex Hospital in July, 1949, under the care of Dr. Beaumont, complaining of joint pains, and the development of bruises. Examination revealed the presence of ecchymoses and petechiae. His platelet count at repeated examinations was found to be 80,000, bleeding time was prolonged at 6¾ minutes. The Hess capillary test was positive and his bone marrow showed scanty megacaryocytes. No cause was discovered for his joint pains and a diagnosis of thrombocytopoenic purpura was made. Three months later he was admitted to our Rheumatic Unit with pyrexia, cold and clammy hands, and typical rheumatic swellings of the interphalangeal joints. His platelet count was then 240,000, and bleeding time was normal, but he refused a further sternal puncture.

Since many clinicians believe that the earliest features of rheumatoid arthritis may well be explained on the basis of undue capillary fragility, it is interesting to speculate on the relationship of the hypersplenism in this patient to the development of his rheumatoid arthritis and his subsequent recovery after splenectomy.

Pathological Reports on Spleen and Liver

(1) *Mrs. H.*, aged 50, chronic polyarticular arthritis. Spleen shows non-specific hyperplasia. There is hyperplasia of the malpighian corpuscles with enlarged Fleming's centres, many of which contain eosinophilic material. The increase in the pulp is less marked and many of the sinusoids are empty.

(2) *Mrs. N.*, aged 36, polyarticular arthritis. Spleen shows hyperplasia of the pulp.

FIG. 1.—Case 6, low-power view showing hyperplasia of Malpighian corpuscles.

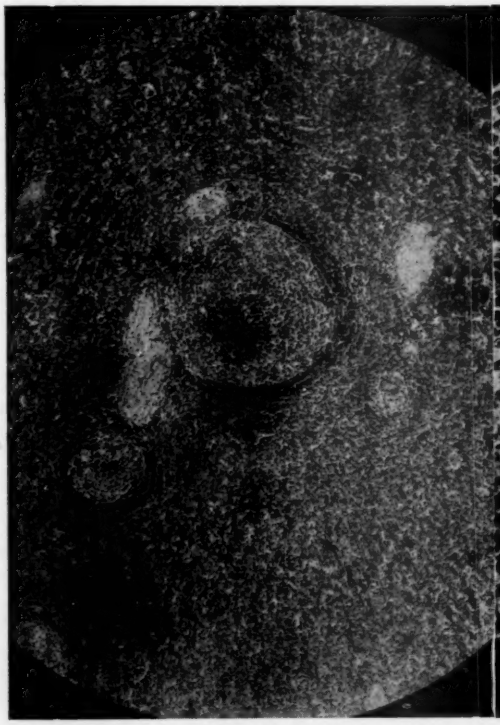

FIG. 2.—Case 6, hyperplasia of the Malpighian corpuscles. Higher-power view.

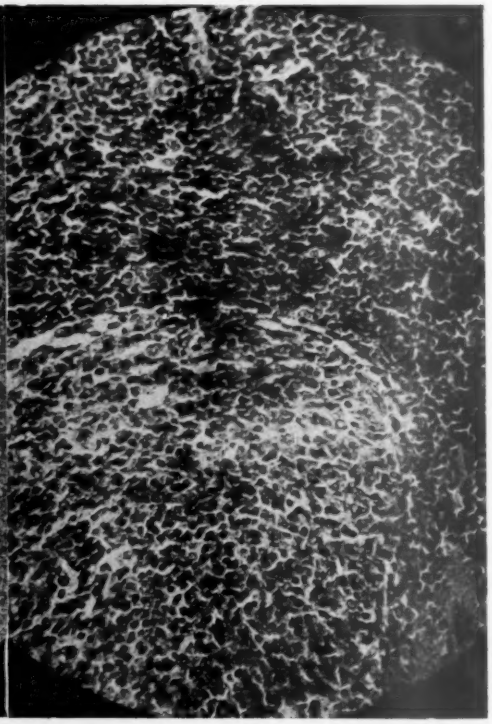

FIG. 3.—Case 6, showing Fleming centre surrounded by dense zone of lymphocytes and an outer looser layer of lymphocytes.

There is more marked hyperplasia of the malpighian corpuscles, with enlarged Fleming's centres which are mostly cuffed by reticulum cells. There is eosinophilic material within the centres. There is increased density of the pulp but no increase in fibrous tissue.

(3) *Mrs. C.*, aged 32, polyarticular arthritis. Spleen shows no hyperplasia of the malpighian corpuscles. Pulp shows some hyperplasia with many eosinophils. There is some eosinophilic material in the few malpighian corpuscles showing Fleming's centres. No increase in fibrous tissue.

(4) *Mrs. R. S.*, aged 37, chronic polyarticular arthritis. Spleen shows tremendous lymphatic hyperplasia of the malpighian bodies with large Fleming's centres. Medulla rather fibrous but empty of cells. No increase in fibrous tissue. Amyloid—nil.

Liver shows a thickened capsule, and dilated but empty sinusoids, and cells appear normal. Some early increase is seen in fibrous tissue, mainly peri-portal. Amyloid—nil.

(5) *Mrs. E.*, aged 61, acute polyarthritis. Spleen shows hyaline changes in some of the lymph nodules.

(6) *G.C.*, aged 26, acute polyarticular arthritis. Spleen shows hyperplasia of the pulp and follicles. The Fleming's centres are particularly large and there is albuminoid material in places. No increase in fibrous tissue. Amyloid—nil. (Figs 1, 2, 3.)

Liver shows fatty degeneration around the central venules, but is otherwise normal.

In general, the pathological examinations of the spleen showed non-specific hyperplasia of the malpighian corpuscles, with hyaline changes in the central arterioles in some sections. One case also had excessive activity of the reticulo-endothelial cells of the pulp. There was no evidence of amyloid change in any of the sections.

Comment

Hench and others (1950), later quoted by Davidson (1950), refer to the pathological physiology which constitutes the " fire " in rheumatoid arthritis, and to the pathological anatomy which represents the " ashes " of the disease.

(1) Clinically the disease has been relatively, and in some instances, completely inactive since operation. In no instance has there been a definite flare-up. In some cases, the relief of pain, stiffness, and joint swelling, was immediate, in others, delayed. It is interesting to compare this re-action with that following cortisone and ACTH therapy.

(2) In two cases, there has been a definite progression of articular deformity, judged by clinical and *x*-ray signs. It is possible that the reduction of joint-swelling and the absence of muscle spasm has contributed to this deformity by allowing the patients to use their hands freely and without pain.

(3) Certain features in its pathological physiology have been reversed. Certain of the laboratory findings have returned towards normal after operation. We do not know the significance of certain changes, among them the so-called " hepatic-function tests " and the histological changes seen in the spleen and lymph glands. The evidence on bone-marrow changes, bleeding times, and Splenin A and B, is insufficient to be worthy of report.

When the laboratory findings are compared with those that follow cortisone or ACTH therapy, a similar, but somewhat delayed and less dramatic response is seen. The blood sedimentation rate falls, the haemoglobin increases, and in some cases there is an increase of the red-cell count. The white-cell count also increases, and when the serum protein total and albumin globulin ratio is abnormal it tends to return to normal. The hepatic-function tests, when abnormal, tend to improve with the serum protein tests.

We make no claims for this form of therapy which we consider entirely experimental in nature, especially as we have no similar series of rheumatoid arthritis patients who have been operated on for other reasons for comparison. However, we hope that the follow-up of these patients may help to throw some light on the effect of splenic function on the progress of rheumatoid disease.

Summary

The case histories and follow-up are presented of twelve patients suffering from rheumatoid arthritis in whom the spleen had been removed at some time during the previous 12 years.

After operation, the disease, judged by the clinical picture, had become completely or relatively inactive. There was improvement of general health, with relief of pain, joint stiffness, and joint swelling. Laboratory findings showed a reversal of certain features in the pathology of the disease.

These findings are compared with those known to follow cortisone and ACTH therapy. A brief historical review is given, and evidence presented, to show why the spleen is considered to be an endocrine gland. The inter-relationship between the spleen, pituitary, ovaries, bone marrow, and adrenal cortex is discussed. The removal of the spleen in rheumatoid arthritis is not advocated, but the need for a further study of the spleen and bone marrow in their relationship to this disease is strongly emphasized.

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Splénectomie dans l'Arthrite Rhumatismale

RÉSUMÉ

Les auteurs présentent les observations de douze cas d'arthrite rhumatismale chez qui la rate avait été enlevée au cours des douze dernières années.

Après l'opération, la maladie, jugée d'après son aspect clinique, devint complètement ou relativement inactive. L'état général s'améliora et la douleur, la rigidité, et la tuméfaction articulaires s'atténuèrent. L'examen de laboratoire révéla l'inversion de certains éléments pathologiques.

On compare ces résultats à ceux qu'on obtient généralement avec la cortisone et l'ACTH.

Les auteurs passent en revue l'histoire du problème et donnent leurs raisons de considérer la rate comme une glande endocrine. Ils discutent les rapports existants entre la rate, l'hypophyse, les ovaires, la moelle osseuse, et l'écorce surrénale. Sans préconiser la splénectomie dans l'arthrite rhumatismale, ils soulignent la nécessité d'études ultérieures de la rate et de la moelle osseuse par rapport à cette maladie.

Esplenectomía en Artritis Reumatoide

SUMARIO

Los autores presentan la historia clínica de doce casos de artritis reumatoide en los cuales se había efectuado la esplenectomía en algun período comprendido en los últimos doce años.

Después de la operación, la enfermedad, juzgando por el cuadro clínico, había devenido en completa o relativamente inactiva. El estado general había mejorado, constatándose atenuación de dolor, de rigidez, y de tumefacción articulares. Los exámenes de laboratorio revelaron la inversión de ciertos elementos patológicos de la enfermedad.

Se efectúa una comparación de estos resultados con aquellos que reconocidamente suceden al tratamiento con la cortisona y la ACTH. Los autores efectúan una breve revisión histórica y presentan evidencias demostrativas del por qué consideran el bazo como una glándula endocrina. Se discute la inter-relación entre el bazo, la pituitaria, los ovarios, la médula ósea, y la corteza suprarrenal. Sin preconizar la esplenectomía en la artritis reumatoïde, los autores acentúan enfáticamente la necesidad de estudiar ulteriormente el bazo y la médula ósea en relación con esta enfermedad.

COPPER TREATMENT OF EXPERIMENTAL AND CLINICAL ARTHRITIS*

BY

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Since 1940 copper salts have been used experimentally in the treatment of a variety of diseases. Goralewski (1940), Tüchler and Ranzenhofer (1940), and Arold (1940), used copper salts in the treatment of pulmonary tuberculosis. Forestier (1944, 1949), Forestier and Certonciny (1946, 1949), and Forestier and others (1948, 1950), popularized the use of organic copper salts in rheumatic diseases. Since the use of gold salts in rheumatoid arthritis carries the risk of toxic manifestations, it was desirable to find other chemical agents of lesser toxicity, and the copper salts were first used with this thought in mind.

The two principal organic salts of copper which have been used in rheumatic diseases are Cupralène† (m'allyl-cuprothiourea sodium benzoate) and Dicuprène‡ (cupro-oxyquinoline-diethyl-sulfonate). Cupralène is administered intravenously since its *p*H is 7·58; it contains 19 per cent. copper and is water-soluble. The usual dosage schedule is twice weekly (0·25 to 0·50 g.) with a total of 2 to 5 g. per series. Dicuprène contains 6·5 per cent. copper and is dispensed in an aqueous solution of *p*H 6·40; it may be given intramuscularly or intravenously (0·5 to 1·0 g.) 2 or 3 times weekly to a total of 6 to 12 g. per series.

Previous Investigations

Forestier and others (1950) claimed a beneficial response in rheumatoid arthritis of recent origin when copper salts were used therapeutically. He noted little toxicity and advocated their use as an adjunct in gold therapy for rheumatoid arthritis. His results were best in patients whose disease was of less than 1 year's duration and in whom copper salts constituted the initial therapy. When the duration of disease was less than one year, the clinical improvement was " greatly improved " and " moderately improved " in 72 per cent. of cases. When treatment was begun after the disease had been present for more than one year, only 40 per cent. were " improved " or " greatly improved ". When copper was used

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† Cupralène, manufactured by Société d'Expansion Chimique, Paris, was the gift of Merck and Co. Inc., Rahway, N.J., U.S.A.

‡ Dicuprène, manufactured by Union Chimique Belge, Brussels, was the gift of E. Fougera and Co., New York.

in patients resistant to gold therapy, only 21 per cent. were "improved" or "greatly improved". In those instances where copper was used after the patient had manifested an intolerance to gold, 50 per cent. "improved".

Tyson and others (1950) evaluated Cupralène in twenty patients whose disease had lasted one to 15 years, and in seven whose disease had lasted 2 months to one year. They reported no benefit in the first group with total doses ranging from 3·8 to 11·2 g. Two patients in the second group achieved remission but both relapsed in less than 6 months. They reported mild toxic effects, including transient, microscopic pyuria and albuminuria, occasional deep pain in the arm and shoulder following injection, thrombosis of the antecubital vein (in three instances), occasional nausea, vomiting, and chills, and several instances of anaemia which promptly returned to normal after discontinuing copper therapy. They also noted the garlic-like odour and taste experienced immediately after intravenous injection.

Forestier and Certonciny (1949) further reported the favourable effect of the organic salts of copper in chronic gouty arthritis. Graber-Duvernay and Van Moorleghem (1950) used an intravenous colloidal suspension of copper morrhuate in 117 cases of chronic rheumatoid arthritis and reported improvement in only 30 per cent. They noted little toxicity when using this suspension intravenously, but on intramuscular injection added procaine because of pain at the site of injection.

Present Studies

The purpose of our investigations was threefold: first, to evaluate Dicuprène and Cupralène in rheumatoid arthritis, rheumatoid arthritis with psoriasis, Reiter's syndrome, ankylosing spondylitis, and chronic gouty arthritis; second, to evaluate these substances in the experimental polyarthritis of rats; and third, to observe their toxic effects in man and rodents.

Evaluation in Treatment of Rheumatic Disease

Rheumatoid Arthritis.—Thirty-one patients (7 males and 24 females) were treated with a total dosage varying from 2·2 to 17·0 g. with injections given 2 or 3 times weekly (Dicuprène intravenously or intramuscularly, and Cupralène intravenously). Twenty-seven received Dicuprène and four Cupralène. The results are shown in Table I (overleaf), the patients being classified according to the extent of the arthritis and the degree of therapeutic response, according to the system outlined by Steinbrocker and others (1949) and advocated by the American Rheumatism Association.* Of the 31 patients treated, only six fell into Groups I and II and 25 were in Grades III and IV as judged by therapeutic response. Therefore, only 19·5 per cent. appreciably improved, fewer than Short and Bauer (1948) observed when only simple supportive therapy was used.

Psoriasis with Arthritis.—Among nine patients (2 males and 7 females) with psoriasis and associated rheumatoid arthritis, the number responding with Grade I or II improvement was 55·5 per cent. (see Table II, overleaf). In this group one patient received

* Grade I: complete remission.

Grade II: major improvement in which the sedimentation rate may still be moderately elevated but in which there is absence of systemic signs of activity such as leukocytosis and fever. There are no signs of joint inflammation although minimal changes due to irreversible capsular thickening may be present and no new rheumatoid process is present.

Grade III: minor improvement not considered significant since the disease has the inherent capability of variation in signs and symptoms. In this grade, however, are all those whose slight improvement prevents them from being Grade IV, and is yet so small that they cannot be Grade II.

Grade IV: no therapeutic response.

TABLE I
COPPER SALTS IN RHEUMATOID ARTHRITIS

Extent of Arthritis		Therapeutic Response (grade)				Total Patients
Stage	Class	I	II	III	IV	
I	1					
	2			2	3	5
	3	1				1
	4					
II	1					
	2	1	2	2	2	7
	3		2	2	1	5
	4				1	1
III	1					
	2			1	2	3
	3			1	1	2
	4					
IV	1					
	2			1	2	3
	3				2	2
	4				2	2
Total Patients		2	4	9	16	31
Percentage in each Grade		6·5	13	29	51·5	100

Only one case became worse.

Cupralène and the others, Dicuprène. No exacerbation of skin lesions was observed during treatment and generally they become less extensive.

Ankylosing Spondylitis.—Among three male patients with ankylosing spondylitis, the results of treatment with Dicuprène were not significant. One showed a therapeutic response of Grade I, a second Grade III, and a third Grade IV.

Chronic Gouty Arthritis.—In this group eighteen patients (16 males and 2 females) were treated. Eight (44·4 per cent.) showed a therapeutic response of Grade I or II; whereas 27·8 per cent. showed no appreciable improvement. Seventeen were treated with Dicuprène and one with Cupralène. These patients also continued to receive coated tablets of sodium salicylate, colchicine, and glycine (gelatin) daily, as they had been doing before the administration of copper salts, and they continued to complain of chronically swollen, painful joints and to have occasional acute exacerbations involving one or more joints. During the copper therapy, only one patient developed a severe exacerbation, and this was promptly controlled by cortisone. In the following year, six patients had acute exacerbations, but for the group generally, exacerbations have been less frequent and less severe. The results are shown in Table III (overleaf).

TABLE II
COPPER SALTS IN PSORIASIS WITH ARTHRITIS

Extent of Arthritis		Therapeutic Response (grade)				Total Patients
Stage	Class	I	II	III	IV	
I	1					
	2	1	1			2
	3					
	4					
II	1					
	2		1		3	4
	3		1		1	2
	4					
III	1					
	2		1			1
	3					
	4					
Total Patients		1	4	0	4	9
Percentage in each Grade		11	44·5	0	44·5	100

Seven of nine patients were females.

(It should be noted that the rating system for therapeutic response was devised for rheumatoid arthritis and its application in gouty arthritis is not to be compared with the series on rheumatoid arthritis but with other series on gouty arthritis.)

Reiter's Syndrome.—Three cases of Reiter's syndrome (2 males and 1 female) were apparently cured after the use of Dicuprène. In each of these, positive cultures for pleuropneumonia-like organisms were obtained from the conjunctivae and in the males from the penile sores and urethral discharge.

Disseminated Lupus Erythematosus.—Grade III response to Dicuprène (one case).

To sum up, Table IV (overleaf) shows that in rheumatoid arthritis the use of copper salts is apparently without benefit. In chronic gouty arthritis, the results are probably worthy of further study. In psoriasis with arthritis, a majority of cases showed improvement in arthritic manifestations and the skin lesions generally were ameliorated. In ankylosing spondylitis the results were insignificant. In Reiter's syndrome (a self-limiting disease), all cases responded favourably. In the one case of lupus erythematosus treated, the result was only slight improvement. Tables I, II, and III show that the patients who improved under treatment were in the less severe stages of each disease. Among those with rheumatoid arthritis treated with cortisone prior or subsequent to copper therapy, twelve out of fourteen had enjoyed a Grade I or II response and two had shown Grade III improvement; whereas under treatment with copper, one patient had a Grade I, two a Grade III,

TABLE III
COPPER SALTS IN CHRONIC GOUTY ARTHRITIS

Extent of Disease		Therapeutic Response (grade)				Total Patients
Stage	Class	I	II	III	IV	
Mild	1					
	2	2	3	1	1	7
	3					
	4					
Moderate	1					
	2				3	3
	3	1				1
	4					
Severe	1					
	2			1		1
	3			2	1	3
	4		2	1		3
Total Patients		3	5	5	5	18
Percentage in each Grade		16·6	27·8	27·8	27·8	100

TABLE IV
THERAPEUTIC RESPONSE TO ORGANIC COPPER SALTS
(Irrespective of Stage and Class)

Disease	No. of Cases	Per cent. Cases			
		I	II	III	IV
Rheumatoid Arthritis	31	6·5	13	29	51·5
Chronic Gouty Arthritis	18	16·6	27·8	27·8	27·8
Psoriasis and Arthritis	9	11	44·5	0	44·5
Ankylosing Spondylitis	3	33·3	0	33·3	33·3
Reiter's Syndrome	3	100	0	0	0
Lupus Erythematosus	1	0	0	100	0

and eleven a Grade IV response. This favourable therapeutic response to cortisone demonstrates the relative inferiority of the copper salts.

Clinical Toxicity.—The toxicity of these substances is slight.

Cupralène.—In all instances, the intravenous administration of Cupralène promptly resulted in garlic-like odour of the breath. This suggests its use in determining arm-to-lung circulation time, particularly since the garlic odour is not present before injection.

This odour persisted in some instances for as long as 8 to 10 hours after injection. If Cupralène escaped from the vein, intense pain and necrosis followed.

Dicuprène.—On intramuscular injection there was marked pain in many patients; so that in the later phases of the study this material was only given intravenously. There was no garlic-like odour of the breath. Three patients developed amenorrhoea while taking Dicuprène but menstruation was resumed after cessation of medication, and one became pregnant. This non-gravid amenorrhoea perhaps reflects an endocrine action.

Occasionally patients complained of slight, transient nausea after the injection of either Dicuprène or Cupralène. Transitory nausea and vomiting occurred in three patients, diarrhoea in one, vertigo in two, and increased stiffness in two. Pigmentation of the skin with pruritis occurred in one, and marked, transitory exacerbation of symptoms occurred in another after a single injection. The total number of reactions noted in relation to the large number of injections given in these groups of patients indicates a low order of toxicity. No change was noted in the blood counts or urinary findings on frequent examinations.

Experimental Arthritis.—An evaluation of Cupralène and Dicuprène was made in the experimental polyarthritis of rats. This arthritis was produced by the intraperitoneal injection of 2 ml. of a broth culture of the L_4 strain of the pleuropneumonia-like organism, as described by Tripi and others (1949). The rat polyarthritis is prevented or cured by the use of gold salts and is used in the laboratory as a means of comparing various substances with gold. Kuzell and Gardner (1950), and Kuzell and Mankle (1950), have indicated that terramycin and aureomycin will also prevent or cure this laboratory polyarthritis, but that various substances, including cortisone, ACTH, pregnenolone, and glutathione, will not prevent its development and even appear to aggravate its extent. Evaluation of the effect of the agents tested was made regarding per cent. survival, incidence of joint involvement, and extent of arthritic involvement scored numerically (" arthrogram score "*) for each group and its controls. The method of arthrogram scoring was described in this Journal by Tripi and others (1949). Since the pathogenicity of each sub-culture varies, it was necessary to run controls for each experiment. Further, the copper salts were tested for curative properties once the arthritis was at its peak, and for preventive properties when medication was begun at the time of the infection.

Cupralène.—Twenty male and twenty female 100-g. albino rats were infected, and beginning on the day of the infection half of each group was given 5 mg. per kg. bodyweight of Cupralène intramuscularly for 2 days and thereafter twice weekly for 7 weeks. Among the treated animals, the incidence was 95 per cent., survival rate 70 per cent., and average arthrogram score (taken at the peak of the joint involvement) 3·5 for males and 3·0 for females. For the controls the comparable figures were 90 per cent., 45 per cent., 4·0 for males, and 3·1 for females.

* The " arthrogram " is a scoring device for calculating numerically the extent of joint involvement in the individual animal, using a scoring system based on 0 to 4 for each anterior extremity, and 0 to 5 for each posterior extremity, thus giving a possible score from 0 to 18. 0=no demonstrable signs of arthritis; 18=all four extremities involved to a maximum degree.

This method of scoring is purely arbitrary and is intended as a rough quantitative clinical estimation of macroscopic joint involvement. The average arthrogram score for the group is calculated by dividing the totals for the individual animals by the number of animals in the group. The averages are computed at various intervals so that the peak of joint involvement may be noted (see Tripi and others, 1949).

Ten male and ten female 100-g. albino rats were treated with 5 mg. per kg. bodyweight of Cupralène intramuscularly beginning the day of the infection, and thereafter 5 days per week to a total of eighteen injections. Among the treated rats the incidence was 95 per cent., survival rate 70 per cent., and average arthrogram score 6·45. Among twenty controls the comparable figures were 95 per cent., 45 per cent., and 6·95.

Ten male and ten female 100-g. rats were given 20 mg. per kg. Cupralène intramuscularly, beginning the day of infection, and thereafter twice weekly for 3 weeks. The incidence was 70 per cent., survival rate 100 per cent., and average arthrogram score 2·25. Among twenty controls the figures were 65 per cent., 100 per cent., and 2·9.

Twenty female 100-g. rats were given 5 mg. Cupralène intraperitoneally on the day after infection and twice weekly for 7 weeks. In the medicated animals the incidence was 80 per cent., survival rate 90 per cent., and average arthrogram score 3·3. In twenty female controls the comparable figures were 60 per cent., 100 per cent., and 2·5.

Dicuprène.—Nine male and ten female 100-g. albino rats were given 20 mg. per kg. bodyweight Dicuprène, and nine males and nine females were given 40 mg. per kg. bodyweight. Dicuprène intramuscularly beginning 11 days after infection and for 10 days thereafter. In the first group the incidence was 68 per cent., survival rate 95 per cent., and average arthrogram score 3·5. In the second group the figures were 83 per cent., 100 per cent., and 4·8. Among nine male and nine female controls, the comparable figures were 72 per cent., 100 per cent., and 3·2.

Eight male and nine female 100-g. albino rats were given 5 mg. per kg. bodyweight Dicuprène beginning on the day of infection and for 12 days thereafter, and nine males and nine females were given 10 mg. per kg. in the same manner. In the first group the incidence was 76 per cent., survival rate 100 per cent., and average arthrogram score 3·8. In the second group the comparable figures were 67 per cent., 54 per cent., and 2·2. In nine male and eight female controls, they were 54 per cent., 87 per cent., and 1·7.

Toxicity in Rats.—Using 347 albino rats of both sexes varying in weight from 100 to 300 g., the LD_{50} for Cupralène given intraperitoneally was found to be 160 mg. per kg. The intraperitoneal use of this material caused extensive adhesions.

The intramuscular administration of Cupralène caused considerable local necrosis and doubtless prevented complete absorption, since the LD_{50} by this method as determined in 45 rats was 375 mg. per kg.

For Dicuprène given intramuscularly the LD_{50} in 100-g. albino rats was 126 mg. per kg., based on administration of the material to fifty animals. There was little local reaction or apparent discomfort following the intramuscular use of Dicuprène.

Discussion

In our clinical experience we were unable to confirm the earlier reports of Forestier and his associates. We did note, however, that those patients showing improvement were generally among the early cases, as they also emphasized. We must keep in mind that these are the cases in which spontaneous remission is also most likely. Our results indicated, as did theirs, that in chronic gouty arthritis, the use of copper salts may be of value and merits further study. In spite of the fact that in rats the use of copper salts was ineffective against the pleuropneumonia-like organism, it was interesting that in three cases of Reiter's syndrome in which pleuropneumonia-like organism was cultured, the use of copper may possibly have effected remission. In the treatment of the arthritis associated with psoriasis the results suggested slightly more improvement than in rheumatoid arthritis without psoriasis, and perhaps here again the results merit further study.

As far as we know no evaluation of serum copper has been made in rheumatoid arthritis and in the studies of the use of copper salts no attention has been paid to this point. Dawson (1950) has studied " the copper protein, ascorbic acid oxidase ", and observed that the enzyme copper undergoes a " reversible oxidation and reduction cycle only when the electron donor (ascorbic acid) and the electron acceptor (oxygen) are both present ". Copper is also a constituent of tyrosine oxidases. The relationships among the different haemocyanins and their relation to copper proteins is not completely understood. Comar (1950) studied the tissue distribution of labelled copper administered to cattle, and found that the tissues showing high concentrations were, in decreasing order: " the liver, kidney, gastro-intestinal tract, adrenals, thymus, gall bladder, and bile." Cartwright (1950) reports that " the oxidation of glutathione, cysteine, ascorbic acid, and glucose is accelerated in the presence of copper ", and that studies in copper deficient animals indicate that copper is " concerned in erythropoiesis, the process of myelinization of the central nervous system, and in the maintenance of normal mammalian pigmentation ". It is also of considerable interest that Fay and others (1949) demonstrated that during normal pregnancy there is an increase in plasma copper. The increase begins in the first trimester and reaches maximum values (more than double the normal) during the last trimester, and in the first 2 months postpartum the plasma copper values regain their normal level. This period of rise in plasma copper levels parallels that of disappearance of symptoms of rheumatoid arthritis during pregnancy. The mere injection of organic copper salts in rheumatic patients will evidently not duplicate this suppression of symptoms, since undoubtedly the increase in plasma copper reflects a change in some other unidentified plasma to which the copper ion is bound.

Summary

(1) Organic copper salts are ineffective in preventing or curing polyarthritis of rats due to the L_4 strain of pleuropneumonia-like organism.

(2) The toxicity of organic copper salts in rats and mice was studied and the LD_{50} found to be high.

(3) A clinical evaluation (using the scoring system advocated by the American Rheumatism Association) of Cupralène and Dicuprène was made in 31 cases of rheumatoid arthritis, three of Reiter's syndrome, three of ankylosing spondylitis, one of lupus erythematosus, eighteen of chronic gouty arthritis, and nine of psoriasis with associated arthritis. These compounds were of no value in the treatment of rheumatoid arthritis and ankylosing spondylitis. Three patients with Reiter's syndrome went into remission. There was questionable benefit in chronic gouty arthritis and in arthritis associated with psoriasis. One case of disseminated lupus erythematosus showed a Grade III therapeutic response. Generally, therefore, copper salts were found to be therapeutically ineffective.

(4) Toxic manifestations due to Cupralène and Dicuprène in 65 patients treated were infrequent, and of a mild, transitory nature.

(5) The garlic-like odour of the breath which follows intravenous administration

of Cupralène suggests its possible use in determining arm-to-lung circulation time.

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Traitement par Sels de Cuivre de l'Arthrite Expérimentale et Clinique

RÉSUMÉ

(1) Les sels organiques du cuivre n'arrivent pas à prévenir ou à guérir la polyarthrite des rats causée par la souche L_4 du micro-organisme du type pleuro-pneumonique.

(2) On a étudié la toxicité des sels organiques du cuivre chez le rat et la souris et on a trouvé que la DM 50 était élevée.

(3) On a procédé à l'évaluation clinique (en se servant du système de notation préconisé par l'*American Rheumatism Association*) de Cupralène et de Dicuprène dans 31 cas d'arthrite rhumatismale, trois de syndrome de Reiter, trois de spondylite ankylosante, un de lupus érythémateux, 18 d'arthrite goutteuse chronique, et neuf de psoriasis compliquée d'arthrite. Ces produits étaient inefficaces dans l'arthrite rhumatismale et dans la spondylite ankylosante. Trois malades avec syndrome de Reiter ont eu une amélioration temporaire. Il y eut une amélioration douteuse dans l'arthrite goutteuse chronique et dans l'arthrite psoriasique. Un cas de lupus érythémateux disséminé a donné une réponse thérapeutique du troisième degré. Les sels de cuivre se sont donc généralement montré thérapeutiquement inefficaces.

(4) Des manifestations toxiques dues au Cupralène et au Dicuprène ont été rares, peu prononcées, et transitoires chez les 65 malades traités.

(5) Une odeur d'ail de l'haleine se dégageant après l'administration intraveineuse de Cupralène fait penser à son emploi pour déterminer la durée de la circulation entre le bras et le poumon.

Tratamiento de la Artritis Experimental y Clínica por Sales de Cobre

SUMARIO

(1) Sales orgánicas de cobre no son efectivas para prevenir o curar la poliartritis producida en ratas por organismos de la cepa L_4 del tipo pleuro-pneumónico.

(2) Se ha estudiado la toxicidad de sales orgánicas de cobre en ratas y ratones y se encontró que la DL 50 era elevada.

(3) Se ha procedido a la valoración clínica (según el sistema de anotación propuesto por la *American Rheumatism Association*) del Cupralène y del Dicuprène en 31 casos de artritis reumatoide, tres de síndrome de Reiter, tres de espondilitis anquilosante, uno de lupus eritematoso, 18 de artritis gotosa crónica, y nueve de psoriasis con artritis asociada. Estos compuestos no fueron efectivos en el tratamiento de la artritis reumatoide y de la espondilitis anquilosante. Tres enfermos con el síndrome de Reiter mejoraron temporariamente. Hubo mejoría dudosa en la artritis gotosa crónica y en la artritis asociada con psoriasis. Un caso de lupus eritematoso diseminado mostró una reacción terapéutica de grado tercero. Las sales de cobre son, pués, sin eficacia terapéutica.

(4) Manifestaciones tóxicas debidas al Cupralène y al Dicuprène fueron raras, benignas y pasajeras en 65 pacientes tratados.

(5) El olor del aliento con resemblanza de ajos que sucede a la administración intravenosa del Cupralène sugiere su empleo para determinar el tiempo de circulación del brazo al pulmón.

RHEUMATOID NODULES

A STUDY IN THEIR PATHOGENESIS AND THE EFFECTS OF CORTISONE AND ACTH

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The dramatic remissions occurring in rheumatoid arthritis during the administration of cortisone or ACTH are now familiar observations. In addition to the volume of clinical and biochemical data already collected, there have been reports describing alterations in the pathological changes of the joint lesions with the use of these drugs. When one of our first cases to receive cortisone showed a rapid disappearance of a rheumatoid nodule over one knee, we became interested in studying the changes produced by hormone administration in these remarkable lesions. Six patients with multiple subcutaneous rheumatoid nodules were given either ACTH or cortisone and detailed observations were made of the effects upon this particular feature of their disease.

This paper presents the clinical and pathological findings which have been of interest; it refers only to the subcutaneous nodules of rheumatoid arthritis.

The Rheumatoid Nodule

The clinical and histopathological features of rheumatoid nodules show definite diagnostic patterns. The nodules are tender, subcutaneous masses, appearing most frequently over the posterior aspects of the forearms. They may be present also about the hands, neck, buttocks, knees, ankles, and feet. They vary from a few millimetres to several centimetres in diameter, and may be freely moveable, or fixed to the skin or to the underlying muscle or periosteum. The larger nodules are frequently composed of a number of smaller ones which have coalesced, and fluctuation may be demonstrated over them.

The aetiology of these lesions is unknown. Not all patients with rheumatoid arthritis develop them, and they have not been described in cases of ankylosing spondylitis of the Marie-Strümpell type. Most authorities agree, however, that trauma plays a very important aetiological role in nodule production, as witnessed by the frequent occurrence of the lesions on the back of the forearms where they rest on the arms of the chair. The influence of trauma was well demonstrated in a patient seen recently, who developed rheumatoid nodules on the right thumb the day after purchasing a new cigarette lighter; the next day he switched the lighter to the other hand and developed a transient nodule in the left thumb.

The histological characteristics of the rheumatoid nodule have been fully described by Klinge (1933), Collins (1937), and Bennett and others (1940), and are considered to be pathognomonic. There are three distinct features:

(*i*) a central zone of necrosis and fibrinoid alteration;
(*ii*) an intermediate zone characterized by palisading of histiocytes and young fibroblasts, together with infiltration of small round cells;
(*iii*) an outer zone composed of fibrous tissue in which there are numerous blood vessels showing various types of alteration (Fig. 1).

In order to understand more fully the changes brought about by ACTH and cortisone, an initial attempt was made to ascertain the detailed pathogenesis of these lesions. For this purpose, a number of specimens were obtained from the patients prior to hormone administration, and several others were taken from the surgical pathology files. Paraffin sections, stained with haematoxylin and eosin, Masson's trichrome, toluidine blue, and the periodic acid-leucofuchsin method of McManus, were studied. All specimens were fixed in 95 per cent. ethyl alcohol.

Although there has been considerable controversy in the past concerning the initial lesions, we would agree with Klinge (1933) that the first changes consist of alterations in the amorphous ground substance of the subcutaneous connective tissue. In the haematoxylin and eosin sections, this is characterized by a mucoid oedematous appearance. There is a spreading apart of the collagen fibres and a fraying of individual fibres apparently due to changes in the ground substance binding together their component fibrils (Fig. 2). Further study using

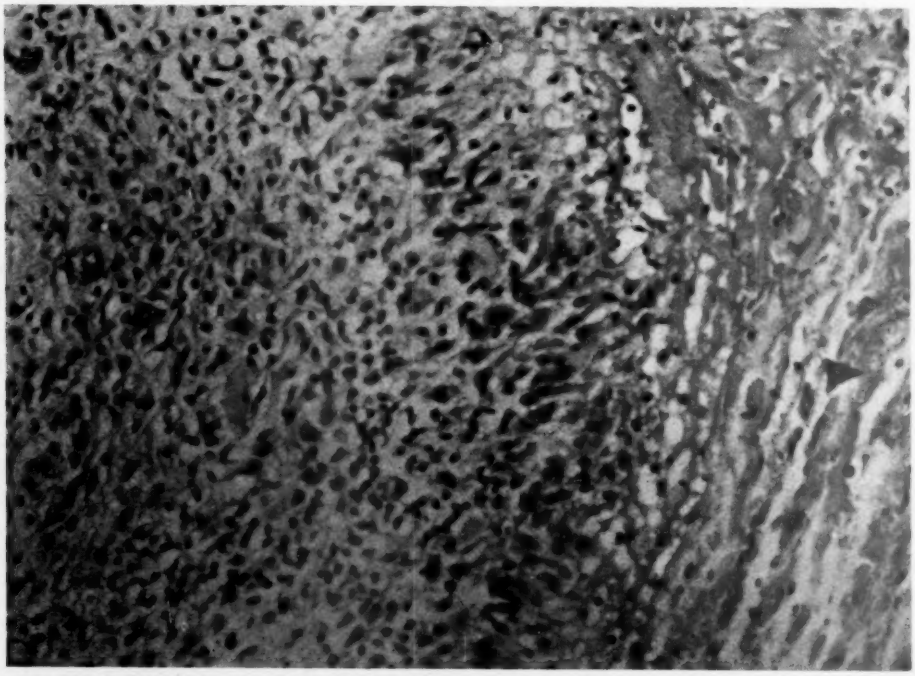

FIG. 1.—Haematoxylin and eosin section demonstrating characteristic features of rheumatoid nodule. Right to left: central zone of fibrinoid alteration and necrosis, palisading of mesenchymal cells, peripheral inflammatory reaction.

toluidine blue stain, however, reveals that the ground substance has not disappeared but has undergone certain alterations which cause the dye to stain metachromatically (Fig. 3). Spatially related to these changes, there appears the fibrillar

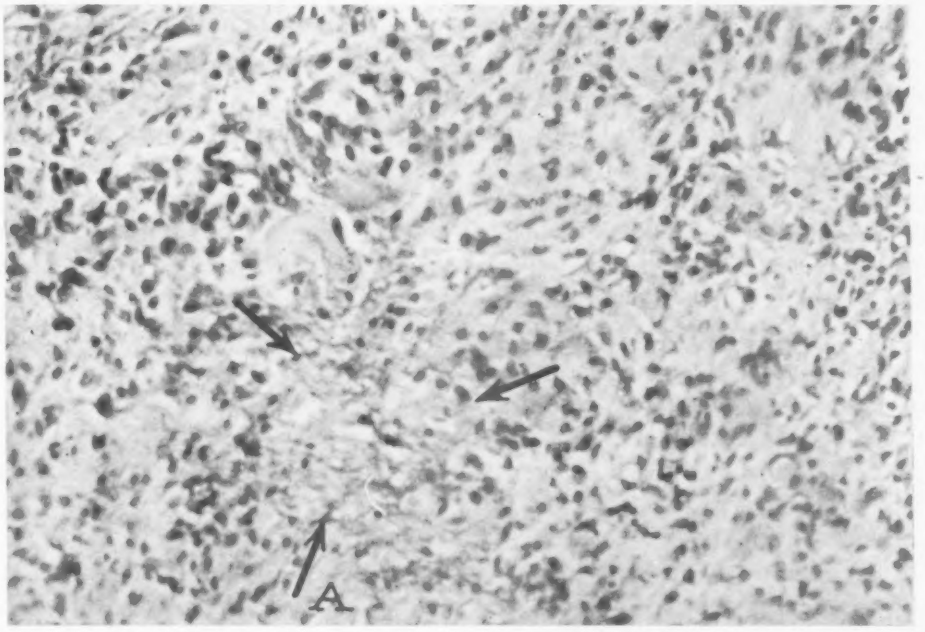

FIG. 2.—Haematoxylin and eosin section demonstrating initial early lesion with area of mucinous oedema and fibrinoid alteration (A) surrounded by granulomatous reaction.

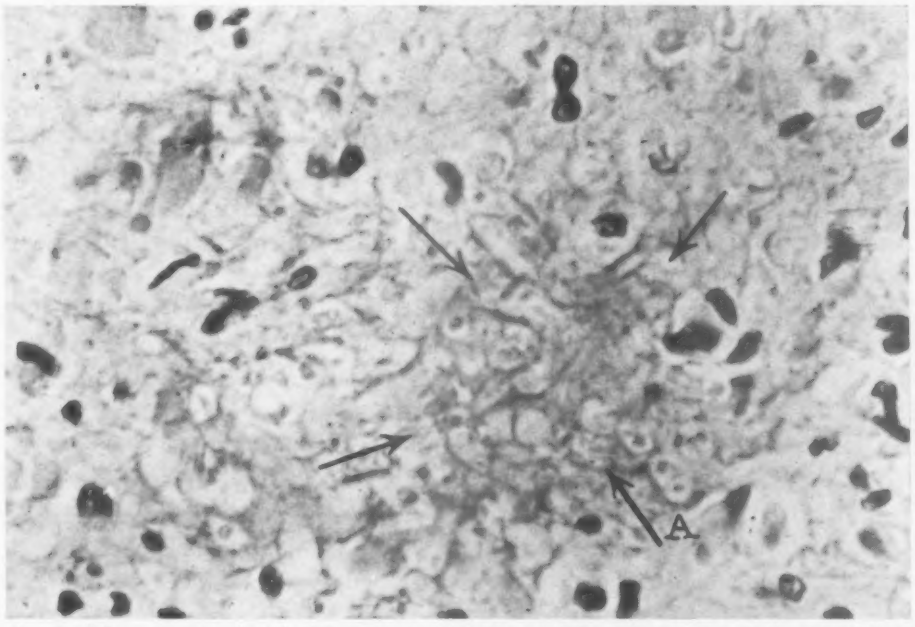

FIG. 3.—Serial section to that in Fig. 2 stained with toluidine blue. The dark material within the arrows represents metachromatic staining of altered ground substance.

eosinophilic substance, fibrinoid. This is the fundamental lesion described in all the so-called collagen diseases.

The present concept of the mode of production of these lesions has been greatly clarified by the recent histochemical work of Altshuler and Angevine (1949). The intercellular amorphous ground substance of normal connective tissue is mucinous in nature, and is composed, partly at least, of acid mucopolysaccharides—mainly hyaluronic acid and chondroitin sulphuric acid. In the collagen diseases, because of the action of various noxious agents, or possibly as a result of an altered immunity mechanism (Aergerter and Long, 1950), it is felt that there is an increased accumulation, or alteration of the mucopolysaccharides, and also a change in the colloidal nature of the ground substance, which becomes less viscous and more oedematous. This increase in acid mucopolysaccharides is demonstrated by the pink or metachromatic staining with toluidine blue dye. It is felt that, while this process is occurring, an alkaline protein, perhaps derived from necrosis of the surrounding tissue, or from the interaction of the tissue with the damaging agent, produces a co-precipitate with the acid mucopolysaccharides, thus forming fibrinoid. As a result of this profound alteration in ground substance, the diffusion of nutrient elements and the elimination of cellular catabolytes may be interfered with, and necrosis of cells takes place.

Associated with these early changes in the rheumatoid nodules, is a proliferative, and to a lesser extent exudative, inflammatory reaction in the surrounding tissues. As the lesion progresses, a further inflammatory change takes place in the region of increasing fibrinoid alteration and cellular necrosis; this consists of a granulomatous proliferation of local fibroblasts and histiocytes to form a palisaded zone about the central area of necrosis—as if in an attempt to wall off the lesion. However, progressive alteration in the intercellular ground substance lying between these newly-formed proliferating cells causes many of the cells to become damaged, die, and become absorbed into the ever-expanding central area. As the process extends, collagen fibres in the area then seem to undergo a non-specific fragmentation, and the fragments can be seen lying free in the central area. The necrotic material in these central areas undergoes liquefaction, and bursa-like cavities may be produced. Often polymorphonuclear leucocytes infiltrate into the cavities, and sometimes, in old, longstanding lesions, large deposits of cholesterol crystals may be seen. In the peripheral zone, in addition to diffuse cellular infiltration, perivascular accumulations of chronic inflammatory cells frequently occur. New blood vessels develop, and marked changes may occur in the vessels themselves, including thrombosis, fibrinoid alteration and necrosis of the vessel walls, and sclerosis.

Thus the final picture is produced: a central zone of fibrinoid alteration, necrosis, and liquefaction, with an ever-retreating surrounding wall of palisaded fibroblasts and histiocytes associated with a chronic inflammatory reaction. Some of the larger, older nodules may show several, smaller, satellite areas in all stages of development. A not uncommon picture is the final coalescence of a number of nodules, some with huge bursa-like central cavities.

Effects of ACTH and Cortisone upon Rheumatoid Nodules

Our observations of the effects of cortisone and ACTH on rheumatoid nodules, agree with those of others who have commented specifically on this subject. Various observers have reported a considerable decrease in the size of the nodules, but not their complete disappearance. No pathological details are available in the literature to date.

Material.—Four of the six patients in this study had well-established severe rheumatoid disease, characterized by multiple severe deformities of peripheral joints, a number of subcutaneous nodules, very high sedimentation rates, and elevated serum globulins. They had not responded to treatment and had been hospitalized for long periods.

The other two cases had much milder disease, without marked deformities, and lower sedimentation rates.

Therapy.—The two milder cases received ACTH intramuscularly and responded satisfactorily to daily doses of 40 and 80 mg. respectively.

Of the four severe cases, two were given cortisone orally, and the other two ACTH intramuscularly. To produce and maintain adequate remissions in these more severe cases, larger dosages of the hormones were required—as much as 200 mg. cortisone or 160 mg. ACTH per day, for weeks at a time. No significant side-effects were observed.

The nodules were removed at varying times during hormone administration, for comparison with specimens taken previously, and other specimens, obtained during the relapse period which followed withdrawal of the drugs, have also been studied.

Results.—The clinical and histopathological changes observed followed a constant pattern; hence a composite description of our results is given rather than an analysis of individual cases.

Clinical.—The patients experienced a dramatic relief from pain and stiffness, as well as a decrease in all the objective signs of joint disease. The sedimentation rates fell with adequate doses of the hormones, but this occurred very slowly in the severe cases, and a plateau appeared to be reached after which there was no further decline. This feature differed from our previous observations of the effects of the hormones on rheumatoid arthritis without nodules, where rapid falls in sedimentation rates to normal were the rule even in the presence of very advanced active disease. The nodules rapidly lost their tenderness and within a few days appeared to be much softer in consistency. On several occasions, a lesion previously considered to be a large single mass could now be felt to be composed of a number of smaller nodules. After 5 to 10 days they began to decrease in size, but, except for one very small nodule in one patient who received ACTH, none disappeared completely (Figs 4 and 5, overleaf). A plateau seemed to be reached after 3 to 4 weeks, and no further changes in the nodules were apparent upon clinical examination thereafter. A rapid increase in the size and tenderness of the nodules followed withdrawal of the drugs.

Histological.—These changes were of considerable interest. Specimens taken only 5 days after starting hormone administration showed almost complete disappearance of the oedema, and of the metachromatic properties of the ground substance at the edges of the central zones. In one case, some metachromasia was still present after 22 days on ACTH, but this was only in the centre of the

FIG. 4.—Patient J.D., male, aged 59, before ACTH. Compare nodules at A and B with Fig. 5.

FIG. 5.—Same patient as in Fig. 4 after 21 days on ACTH. Nodule A has greatly decreased and B has completely disappeared.

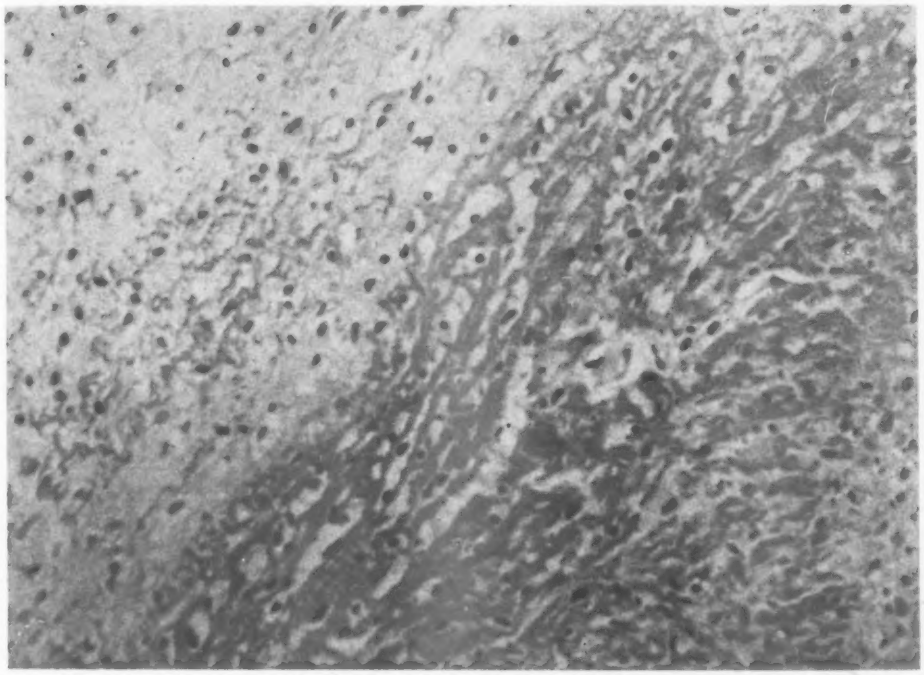

FIG. 6.—Haematoxylin and eosin section of nodule after 5 days on cortisone. Right to left: persistence of fibrinoid alteration and necrosis, complete disappearance of palisading, marked reduction in peripheral inflammatory reaction.
Serial section stained with toluidine blue showed absence of metachromasia.

necrotic material, and did not appear to be related to the fibrinoid. Associated with this there was a striking reduction in the surrounding reaction. The palisading disappeared completely and there was a marked decrease in the inflammatory reaction. Fibrinoid alteration was still present centrally at first, and many degenerating nuclei were intermingled with this material (Fig. 6); these possibly represented cells from the disintegrated palisaded zone. In subsequent specimens even the fibrinoid material had disappeared, and in some instances the central zone was composed merely of old necrotic material and clumps of fragmented collagen fibres (Fig. 7). There was no evidence of destruction of pre-existing fibrous tissue. No acute degenerative abnormalities of the blood vessels were observed in specimens taken during hormone administration.

In the sections of specimens removed after relapse had occurred, striking amounts of metachromatic and fibrinoid material had recurred. Almost the entire specimen would be composed of fibrinoid with very little surrounding reaction and only a beginning of palisading. These changes appeared to be almost fulminating in intensity (Fig. 8).

Comment

The changes demonstrated after hormone administration consist chiefly in alterations of the intercellular substances to produce a more normal state, and in

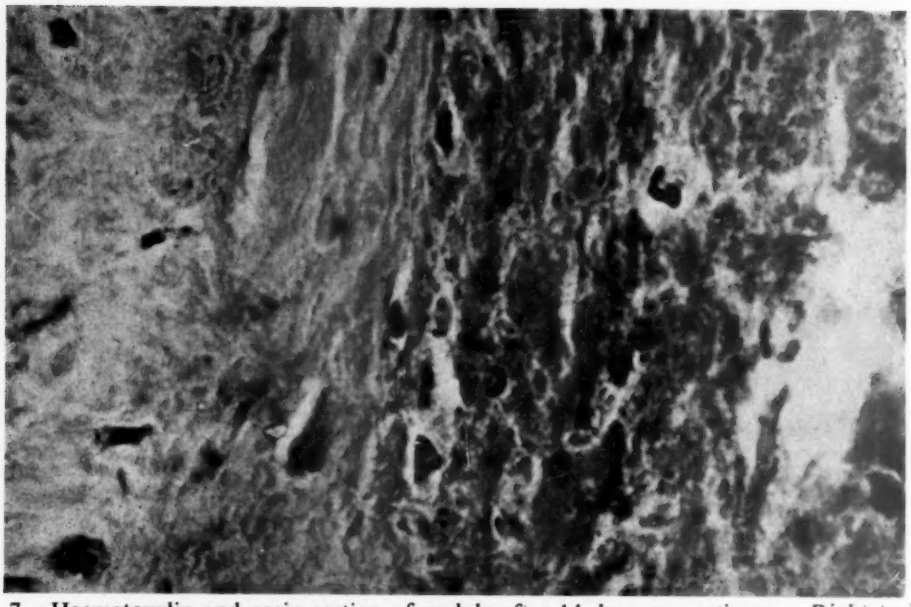

FIG. 7.—Haematoxylin and eosin section of nodule after 14 days on cortisone. Right to left: disappearance of fibrinoid alteration, absence of palisading, absence of peripheral inflammatory reaction. Central zone (on right) shows only amorphous, necrotic, granular material as yet unabsorbed.

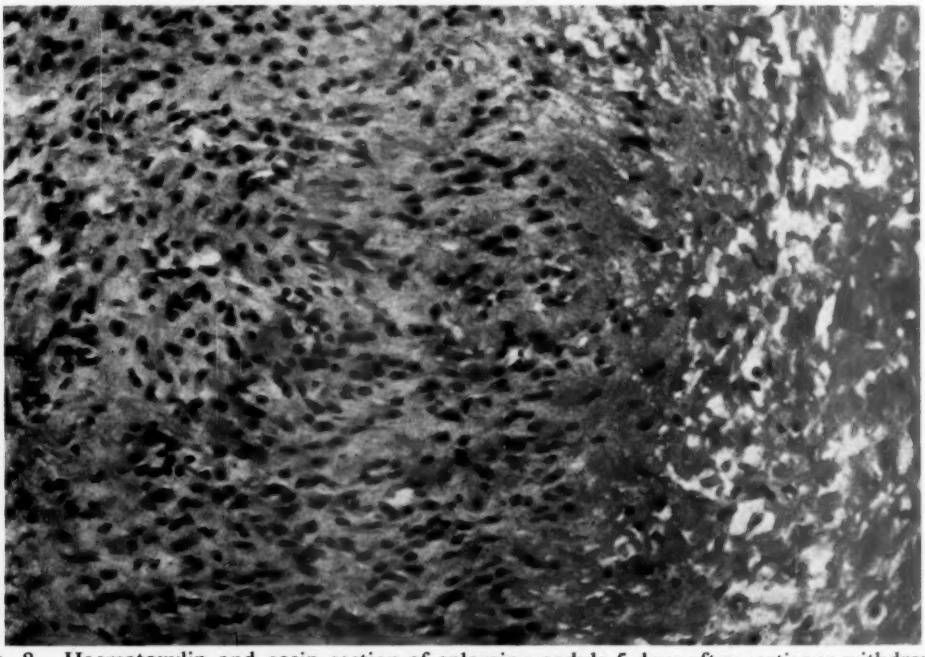

FIG. 8.—Haematoxylin and eosin section of enlarging nodule 5 days after cortisone withdrawal, showing reappearance of fibrinoid (right), but little palisading or inflammatory response so far. Serial section stained with toluidine blue demonstrated reappearance of metachromasia.

a reduction in the proliferative reaction of the intermediate zone in the nodules. The decreased oedema and the reduction in the granulomatous reactions probably

account for the lesions being softer and smaller upon clinical examination. The changes in the ground substance recall the changes demonstrable *in vitro* by the treatment with hyaluronidase of sections showing metachromasia. There is also a similarity to the appearance of granulation tissue in scurvy. In both instances, metachromasia to toluidine blue is absent.

In the case of scorbutic granulation tissue, administration of vitamin C has been shown by Penney and Balfour (1949) to cause the appearance within 12 hours of metachromasia in ground substance with subsequent production of normal granulation tissue. This indicates that vitamin C is necessary for the development of metachromasia in granulation tissues. The thought arises that the changes produced by cortisone or ACTH might be the result of local ascorbic acid deficiency due to hormone administration. No positive opinion can yet be given, but we may refer to the work of Plotz and others (1950), who were unable to block the action of the hormones in their patients by massive doses of vitamin C.

A second possibility which suggests itself is that the hormones may produce a local hyaluronidase-like effect, either directly on the ground substance or by stimulation of the connective tissue cells to produce such an effect. However, Opsahl (1949) has shown that both cortisone and ACTH have an inhibitory effect on the spreading phenomenon induced by hyaluronidase. Hence it would not appear likely that the hormones act through local production of that enzyme.

A third possibility is that the hormones act directly on the connective tissue cells and intercellular substances, somehow protecting them from the action of the injurious agent, and that the chain of events in the ground substance leading to mucinous oedema and fibrinoid precipitation is accordingly inhibited.

Again, the hypothesis has been advanced that the administration of cortisone or ACTH results in a more normal antigen-antibody relationship, thus preventing the noxious influence associated with the altered immunity mechanism discussed by Aergerter and Long (1950). The striking reductions towards normal of certain elevated serum globulin fractions support this idea.

The striking decrease in the proliferative reaction within rheumatoid nodules during ACTH or cortisone administration recalls the observations of Plotz and others (1950) and of Spain and others (1950). These workers noted that the administration of these hormones delayed the appearance of connective tissue in a series of wounds in experimental animals.

In our cases, the hormones may directly inhibit the proliferation of the mesenchymal cells in the palisaded zone, or again, by the blocking or inhibition of the action of the noxious agent, they may remove the stimulus to proliferation. The rapid relapse with recurrence of nodule formation, indicates that the underlying aetiological agent was not eliminated, but that its action was temporarily suppressed.

Summary

(1) In six cases of active rheumatoid arthritis with subcutaneous nodules, the administration of ACTH or cortisone led to a definite softening and shrinkage of the nodules, but, except for one small nodule, the lesions did not disappear.

(2) In four severe cases, the sedimentation rates fell very slowly and incompletely even with large doses of the hormones. This is of interest since in other rheumatoid patients, with disease of similar severity but without nodules, sedimentation rates rapidly fell to normal during the use of these hormones.

(3) The histological changes induced in the nodules consisted of:

(*a*) disappearance of the mucinous oedema of the ground substance and inhibition of fibrinoid alteration;

(*b*) striking reduction in the proliferation of mesenchymal cells in the zone surrounding the central areas of necrosis;

(*c*) no apparent effect on the peripheral zones of fibrous tissue.

(4) Possibilities regarding the mode of action of the hormones are discussed.

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Nodules Rhumatismaux: Étude des Effets de la Cortisone et de l'ACTH

RÉSUMÉ

(1) Dans six cas d'arthrite rhumatismale active avec présence de nodules souscutanés, l'administration de l'ACTH ou de la cortisone mena à un ramollissement notable et à la contraction des nodules mais, à l'exception d'un petit nodule, ces lésions ne disparurent pas.

(2) Dans quatre cas graves, la vitesse de la sédimentation ne diminuait que lentement et incomplètement, même avec de fortes doses de ces hormones. Ceci est d'un intérêt particulier par le fait que dans nos cas de rhumatisme de gravité similaire, mais sans présence de nodules, la sédimentation globulaire se ralentissait rapidement sous l'influence de ces hormones.

(3) Les altérations histologiques subies par ces nodules étaient les suivantes:

(*a*) disparition de l'oedème mucineux de la substance basale, et l'inhibition de la transformation fibrinoide;

(*b*) réduction frappante de la prolifération des cellules mésenchymateuses dans la zone entourant les surfaces centrales de nécrose;

(*c*) pas d'effet apparent sur les zones périphériques de tissu fibreux.

(4) On discute certaines possibilités concernant le mode d'action des hormones.

Nódulos Reumáticos: Estudio de los Efectos que sobre ellos ejercen la Cortisona y la ACTH

SUMARIO

(1) En seis casos de artritis reumatoide activa con presencia de nódulos subcutáneos, la administración de la ACTH o de la cortisona condujo a un notable ablandamiento y contracción de los nódulos pero, con la excepción de un pequeño nódulo, estas lesiones no desaparecieron.

(2) En cuatro casos graves la velocidad de sedimentación eritrocitaria disminuyo muy lenta e incompletamente, aún con dosis fuertes de las hormonas. Esto presenta un interés particular ya que en nuestros casos de reumatismo de gravedad similar, pero sin presencia de nódulos, la sedimentación bajaba rápidamente bajo la influencia de estas hormonas.

(3) Los cambios histológicos inducidos en los nódulos fueron los siguientes:

(*a*) desaparición del edema mucinoso de la substancia basal, e inhibición de la transformación fibrinoide;

(*b*) reducción asombrosa en la proliferación de células mesenquimatosas en la zona periférica de las áreas centrales de necrosis;

(*c*) ausencia de efecto aparente en las zonas periféricas del tejido fibroso.

(4) Se discuten ciertas posibilidades respecto al modo de acción de estas hormonas.

KNEE EFFUSION IN YOUNG ADULTS AS AN EARLY SIGN OF DEGENERATIVE ARTHRITIS

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Three successive undergraduates attending for routine health examination showed signs of a small effusion in the knee joint. This led to the question:

Was such an amount of fluid normal, or was it, as is commonly taught, pathological when sufficient to be demonstrated clinically?

If it was the result of an abnormality, the finding of three successive cases might simply be a rare sequence. Alternatively, the practice of routine examination might bring to light a defect which, though constituting little or no handicap, was nevertheless common. Lastly, if this amount of fluid was in fact normal, its presence would have to be explained by postulating that the quantities present were in the upper part of the normal range of variation, a range which so far as was known had not been studied with precision. Accordingly it was decided to include examination of the knee joint in subsequent routine health examinations until sufficient data became available to form an opinion of the aetiology.

Effusion was demonstrated in 39 of the next 213 young men examined, and in ten of the next 78 women undergraduates. This gives an incidence of 18·3 per cent. in the men and 12·8 per cent. in the women. The discovery of so many effusions came as a surprise to the author and also to others who, hearing of it for the first time, were inclined to doubt the authenticity, or more cautiously to enquire for details, of the method of examination.

Method of Examination

With the subject lying on a couch, his leg slightly everted and knee extended, pressure is first applied and then maintained over the suprapatellar pouch of the knee joint. The outer side of the knee is next stroked by the examiner's free hand from above downwards, using pressure firm enough to invert the leg in the final stage if necessary. In this way fluid, if present in more than small amounts, is made to flow into and to fill out the sulcus on the inner aspect of the knee behind the medial border of the patella. Once seen, the manner in which the fluid flows into the sulcus, like water into a lax balloon, is unlikely to be confused with a bulge of the infrapatellar pad of fat. One is in fact more likely to miss a moderate effusion, especially in an obese subject, because the medial sulcus is obliterated by effusion before examination starts.

A few cases with a recent history of injury or internal derangement of the knee were excluded from the series. No case with effusion was included where any complaint, local tenderness, or other abnormal sign was found. Radiographs were not taken because in the absence of symptoms there was no indication to draw attention to a condition the cause of which was so uncertain.

Examination of Possible Causes

Table I gives the percentage incidence of knee effusion according to possible aetiological factors.

Age.—Among the men higher incidence was found in higher age groups. From 7·2 per cent. at 17-19 years, it increased to 33·4 per cent. in those over 25 years old, a trend which is statistically significant. In comparing those under 22 years of age with those of 22 or more, the difference in percentage incidence divided by its standard error equals 2·74.

Sex.—Only 78 women were examined. Their average age was 19·3±0·13 years (S.D. 1·1). The percentage with effusion (12·8) was lower than in the men, but the average age of the men (22·0±0·19 years) was higher. Because of the small size of the sample a more detailed analysis was not conducted for the women.

Weight.—Higher incidence was found in men weighing 160 lb. or more, compared with those under 160 lb. The difference approaches but does not reach the five-per-cent. level of significance ($\frac{\text{Difference}}{\text{S.E. Diff.}}=1\cdot64$). Further doubt is cast upon the possible importance of weight as an independent aetiological factor when it is remembered that weight increases with age, and the association of effusion with increasing age has already been shown to be more significant.

Size of Articular Weight-bearing Surface in the Knee.—It is not possible to measure the exact size of the weight-bearing articular surface at a routine health examination, but it is believed that this area correlates positively with the bicondylar measurement of the femur. This was available for 190 of the same undergraduates from a routine anthropometric study which was being conducted by Dr. J. M. Tanner and the author. From Table I it may be seen that the incidence of effusion diminished from 24·1 per cent. in those with small bicondylar measurements to 16·0 per cent. in those with large bones. The trend is not significant, but it is suggestive, especially when it is remembered that differences, if any, due to growth, weight gain, or increasing age, would tend in the opposite direction.

Combination of Weight and Width of Femur.—The incidence was next examined according to combinations of weight and bone size. In a group of 48 with smaller bones and greater weight it was 31·3 per cent., and in another group with larger bones and smaller weight it was only 14·9 per cent. This difference in the percentages with effusion is significant ($\frac{\text{Difference}}{\text{S.E. Diff.}}=2\cdot09$) and suggests a mechanical factor leading to greater frequency of effusion where the weight is great and the weight-bearing joint surface small. The average age of the two groups was checked, and the difference in the means (0·4 years) may be regarded as insignificant since the standard error of the whole sample of 190 was 0·21 years. Further subdivision of the two contrasting combinations (smaller bones with greater weight and larger bones with lower weight) into those under 22 years old and those of 22 years or more is interesting. Table II (overleaf) suggests that, although samples are reduced to a level where statistical significance is lost, that age and the mechanical factor are independent. A difference in incidence of 13·2 per cent. in younger subjects, which might be attributed to the mechanical factor, can be compared with 14·7 per cent. in

TABLE I
PERCENTAGE INCIDENCE OF KNEE EFFUSION IN YOUNG MEN, BY POSSIBLE CAUSES

Possible Causes			No. at Risk	With Effusion	
				Number	Per cent.
Age (yrs)	17-19		42	3	7·2
	20-21		71	10	14·1
	22-24		61	13	21·3
	25 or more		39	13	33·4
Weight (lb.)	Small: less than 150		83	12	14·0
	Medium: 150 to 159		57	9	15·8
	Great: 160 or more		73	18	24·6
Age (yrs) and Weight (lb.)	Under 22	less than 150	51	5	9·8
		more than 150	62	8	12·9
	22 and over	less than 150	32	7	21·9
		more than 150	68	19	28·0
Bicondylar Measurement of Femur (cm.)	Small (less than 9·5)		58	14	24·1
	Medium (9·5 to 9·9)		89	17	19·1
	Large (10·0 or more)		43	7	16·3
Smaller bones and greater weight	Small bones, wt. over 150 lb. Medium bones, wt. over 160 lb.		48	15	31·3
Larger bones and smaller weight	Medium and large bones, wt. less than 160 lb.		74	11	14·9
Bones and weight similar	Small bones, small weight		39	7	18·0
	Medium bones, medium weight		30	4	13·3
	Large bones, great weight		29	5	17·3
Physical Constitution (Sheldon's metric types)	Endomorphs		21	6	28·8
	Mesomorphs		74	11	14·9
	Ectomorphs		51	13	25·0
	Midrange types		36	7	19·4
Athletic Injury	Contact sports		65	13	20·0
	Non-contact sports		91	17	18·7
	Misc. light exercise or nil		87	14	16·1
Socio-Economic Factors	Ex-boarding school		72	11	15·0
	Ex-elementary school		73	16	22·0
Total Young Men Examined			213	39	18·3

older subjects. The differences which might be attributed to age in each separate combination of bone size and weight are similar (8·3 and 6·8 per cent.). Lastly, there were four subjects with effusion in a small but extreme group of eight whose bicondylar measurements were less than 9·5 cm. but whose weight exceeded 160 lb.

Other Factors Examined

Physical Constitution.—Body type had already been determined in this series of young men (using Sheldon's photographic and metric technique), and the data were therefore examined for evidence of constitutional disposition to knee effusion.

TABLE II
INCIDENCE OF KNEE EFFUSION IN YOUNG MEN, BY AGE, BONE SIZE, AND WEIGHT

Age (years)	17-21	22 and over
Small bones, weight over 150 lb. .. .. .. Medium bones, weight over 160 lb.	4/16 (25·0 per cent.)	10/30 (33·3 per cent.)
Medium bones, Large bones, } weight less than 160 lb. ..	5/42 (11·8 per cent.)	6/32 (18·6 per cent.)

Exact definitions of the constitutional types have been given by Sheldon and others (1940), but for present purposes it is enough to indicate that endomorphs are usually fat men in middle age, mesomorphs are muscular men with heavy bone structure, and ectomorphs are those men whose weight is small in proportion to their height. Midrange somatotypes are found near the centre of the general distribution of physical types. The lowest incidence of effusion was found in 74 mesomorphs, and the difference in proportion between mesomorphs and other types with effusion approaches statistical significance ($\frac{\text{Difference}}{\text{S.E. Diff.}} = 1 \cdot 57$). The difference could have arisen by chance, though the odds favour it not doing so. On the other hand, two of the characteristics of mesomorphs described by Sheldon are (*a*) that their bones are broad, and (*b*) that their body ratio height/cube root of weight is seldom less than 12·5, that is, their weight is seldom so excessive in proportion to their height as it commonly is in fat men. The bones of endomorphs, as of ectomorphs, tend to be slender. Once again the mechanical factor is suggested. Constitutional study does not appear to assist understanding beyond this point.

Sport.—Men playing rugger, soccer, and hockey were grouped together as taking part in contact sports. Rowing men, cross-country runners, and other athletes (including those who cycled for recreation) were grouped as taking part in non-contact sports. The remainder took miscellaneous light exercise or virtually no regular outdoor exercise at all. The slightly higher incidence of effusion (20 per cent.) in those taking part in contact sports is not significant.

Socio-Economic Factors.—An attempt to gauge socio-economic factors was made by dividing the subjects into those whose early circumstances permitted boarding-school education as distinct from Government-aided primary education. The difference of 7 per cent. is not significant.

Discussion

To summarize findings thus far, two factors show a significant association with effusion in the knee. These are age and a mechanical factor which involves more than average weight being borne by bones of narrow cross section. These findings render it unlikely that the effusions consist of normal synovial fluid. The evidence that repeated injury to athletes is important in the aetiology is negligible and no known infectious process would account for so high a rate of incidence in the sample as a whole. If trauma and infection are both unlikely causes, then degenerative lesions may next be considered. Osteo-arthritis is recognized as

common in middle and old age, especially in the weight-bearing joints of overweight people. At this time of life medical aid is sought on account of pain or other handicap, and the onset of disability rather than the onset of the degenerative process has received the greater attention. However, Gray (1948) reported the occurrence of chondromalacia patellae in a series of young subjects and discussed the surgical treatment of those already suffering severe or prolonged disability. Øwre (1936) reported degenerative changes in the knee joint found at *post mortem* in 27 of 32 subjects between 20 and 29 years of age, and Bennett and others (1942) confirmed this observation and the fact that degenerative change increased with each decade. Such changes commonly start even before growth ceases. There is, therefore, clear pathological evidence that degenerative changes occur with great frequency in the knee joint of young adults, and it seems probable that the clinical significance of a small effusion is related to these changes. The sign naturally passes unnoticed by subjects who are otherwise healthy and who unless they complain of knee trouble are not likely to have their knees examined.

Prevention of Osteo-Arthritis of the Knees

Complete prevention of osteo-arthritis seems no more likely than prevention of the process of ageing. On the other hand, if the clinical sign of a small knee effusion by itself is accepted as an early indication of osteo-arthritis, this may lead to weight supervision, and if necessary to weight reduction or other preventive measures being adopted earlier and with better chance of success. Obesity commonly occurs in association with femurs of small bicondylar measurement and it is here that the risk of effusion is greatest. This agrees with the general clinical impression that in middle age osteo-arthritis is especially common in obese patients.

Summary

(1) Knee effusion was demonstrated by clinical examination in 18·3 per cent. of 213 young men, and in 12·8 per cent. of 78 young women undergraduates, at consecutive routine health examinations.

(2) Examination of possible causes in the men showed a significant increase in the prevalence of effusion in association with age, but an increase in prevalence in association with weight did not reach the 5 per cent. level of significance.

(3) The weight-bearing surface area in the knee joint was assessed by measurement of the bicondylar width of the femur. In a group of 48 men with smaller bones and greater weight the prevalence of effusion was 31·3 per cent., while in another group with larger bones and smaller weight the prevalence was only 14·9 per cent. This difference is significant and suggests a mechanical factor leading to effusion where weight is great and weight-bearing joint surface small.

(4) Effusion was not associated to a significant degree with contact sports, nor is any known infectious process likely to account for a high rate of prevalence. The possibility of degenerative changes is therefore reviewed. *Post-mortem* examination shows a majority with degenerative changes in the knee joint before the age of 30, and the clinical sign of effusion is probably related to these changes.

(5) The sign naturally passes unnoticed in healthy subjects, but if it were accepted as an early indication of osteo-arthritis, its recognition could lead to weight supervision or other preventive measures being adopted at any earlier stage.

Besides my debt, already mentioned, to Dr. J. M. Tanner for certain bicondylar measurements of the femur, I wish to acknowledge the statistical assistance of Mrs. C. C. Standley and Miss S. Wilkinson who checked the analysis.

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Epanchement dans le Genou chez de Jeunes Adultes comme Signe Précoce d'Arthrite Dégénérative

RÉSUMÉ

(1) On a constaté un épanchement dans l'articulation de genou chez 18,3 pour cent de 213 jeunes gens, et chez 12,8 pour cent de 78 jeunes étudiantes, au cours d'examens médicaux réguliers.

(2) A l'étude des causes possibles chez les hommes on a trouvé que la fréquence de l'effusion augmentait d'une manière significative avec l'âge, mais comparé au poids elle n'atteignait pas 5 pour cent du chiffre significatif.

(3) La surface portante de l'articulation du genou fut déterminée par la mesure de la largeur bicondylaire du fémur. Pour un groupe de 48 hommes avec des os plus petits et un poids plus grand la fréquence de l'épanchement était de 31,3 pour cent, tandis que pour un groupe avec des os plus grand mais d'un poids moindre la fréquence n'était que de 14,9 pour cent. Cette différence significative fait penser à un facteur mécanique menant à une plus grande fréquence d'épanchement là où le poids est grand et où la surface articulaire portante est petite.

(4) L'épanchement n'était pas associé d'une manière significative à des sports de contact; de même, aucun processus infectieux connu ne semble être responsable de la fréquence aussi élevée. On reconsidère, par conséquent, la possibilité d'altérations dégénératives. A l'autopsie on voit dans la majorité des cas des altérations dégénératives de l'articulation du genou avant l'âge de 30 ans, et il parait probable que le signe clinique de l'épanchement soit apparanté à ces altérations.

(5) Ce signe n'est évidemment pas remarqué chez des sujets sains, mais si on l'acceptait comme une manifestation précoce de l'ostéoarthrite, sa découverte ménerait au contrôle du poids ou à toutes autres mesures préventives, prises en temps utile.

Derrame en la Rodilla en Adultos Jóvenes como Signo Precoz de Artritis Degenerativa

SUMARIO

(1) Exámenes clínicos rutinarios practicados en jóvenes estudiantes demostraron la presencia de derrame en la rodilla en 18·3% de 213 varones y 12·8 de 78 mujeres.

(2) Al estudiar las causas posibles se encontró que la prevalencia del derrame em los varones aumentaba de manera significativa con la edad, pero no en relación al peso, en cuyo respecto el incremento no alcanzaba la cifra de 5% de significancia.

(3) La superficie soportando el peso en la articulación de la rodilla fué determinada mediante medición de la distancia bicondilar del femur. En un grupo de 48 varones con huesos pequeños y de mayor peso la prevalencia del derrame fué de 31·3%, mientras que en otro grupo con huesos de mayor tamaño y con menor peso del cuerpo la prevalencia fué de sólo 14·9%. Esta diferencia es significativa y hace pensar en un factor mecánico que conduce a mayor frecuencia del derrame cuando el peso es mayor y la superficie de soporte de la articulación, manor.

(4) El derrame no estaba asociado de una manera significativa con las prácticas deportivas, ni se puede atribuir esta alta prevalencia a proceso infectioso conocido alguno. Se revisa, por lo tanto, la posibilidad de cambios degenerativos. Resultados de autopsia muestran una mayoría con cambios degenerativos en la articulación de la rodilla antes de los 30 años de edad y parece probable que el signo clínico de derrame está relacionado con éstos.

(5) Este signo, naturalmente pasa desapercibido en sujetos saludables, pero de ser aceptado como indicación temprana de ósteo-artritis, su reconocimiento pudiera conducir a control del peso o a la adopción de otras medidas preventivas en temprana oportunidad.

GOUT

OBSERVATIONS ON THE EFFECTS OF DRUGS ON PLASMA URIC ACID AND URINARY URIC ACID

BY

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In view of the conflict of opinions on the use of various drugs in gout, the effect of a series of commonly used therapeutic agents on the plasma and urinary uric acid in a series of cases suffering from gout has been investigated. Thirteen patients suffering from classical gout were admitted to hospital and kept under observation. Estimations* of the levels of plasma uric acid (P.U.A.) and urinary excretion of uric acid (U.U.A.) over 24-hour periods were made daily, before, during and after administration of certain drugs which were known, or believed, to influence uric acid levels in the blood and urine. It was hoped that the results might act as a guide for the use of these drugs as therapeutic agents. Those chosen were colchicine, sodium salicylate, glycine, carinamide, cinchophen, and probenecid. Colchicine was chosen because of its undoubted clinical effect, in spite of the absence so far of evidence of its effect on the plasma uric acid level. The literature in connection with glycine has been reviewed by Wrigley (1950). Salicylates were first shown to have an effect on uric acid excretion by Jennings (1937) and cinchophen has been known to have a somewhat similar effect since the work of Nicolaier and Dohrn (1908). The use of carinamide (phenyl methane sulphonanilide), first employed to increase the blood levels of penicillin, was suggested by Professor Heller and Dr. Ginsberg in view of its possible value in reducing the tubular resorbtion of uric acid by the kidneys.

Methods

In the majority of cases, the drugs were given during those periods in which the patients were free of symptoms (interval gout). In some cases, however, an acute gouty attack or mild gouty pains developed during the time of administration or between courses of two preparations. These clinical changes were noted and an attempt was made to relate them to the drugs concerned and to the uric acid levels. Observations on these are discussed later. All the patients received a normal standard diet. The figures set out in the Table represent the average percentage change in the levels of plasma uric acid and urinary excretion of uric acid over a 3-day period during and after the administration of the preparation concerned, as compared with previous control levels. These percentages are also shown diagrammatically in the Figure (overleaf). The interval between the times of beginning each course was 7 days.

From a series of daily control observations, it was considered that the effect of any drug in lowering the plasma uric acid or in increasing the urinary uric acid was only

* Uric acid was estimated by modification of Benedict's method.

TABLE
PERCENTAGE CHANGES IN P.U.A. AFTER ADMINISTRATION AND IN U.U.A. DURING ADMINISTRATION OF FIVE DIFFERENT DRUGS

Case No.	Colchicine		Sodium Salicylate		Glycine		Carinamide		Cinchophen	
	P.U.A.	U.U.A.	P.U.A.	U.U.A.	P.U.A.	U.U.A.	P.U.A.	U.U.A.	P.U.A.	U.U.A.
1	+ 9·6	−16·2	−12	+130	−1·5	−38	−17*	+13*	−28	− 5·1
2	+13·6	+23	−65	+12	−42	+36	—	—	−44	+66
3	+ 5·5	+32·5	−70	− 4	−45	+31·5	—	—	−30	+56
4	− 9·6	0	—	—	—	—	—	—	—	—
5	+25	+70	−20	+32	−11	−19·8	−14·5	+ 6·2	—	—
6	−27·5	+12·5	−67	+56	0	+25·5	− 5·6 −39*	−21 +64*	−51†	+28†
7	−22·5	− 9·1	−17	+72	− 16	+63	+ 7	+46	− 6·8	+37
8	−26	+25	−50	+46	+13·6	+38	− 4·3	+ 9·3	−26†	+24†
9	0	+20	−48	+73	0	+17·6	—	—	−27·5	+78
10	—	—	−56	+58	+50	+36	− 8·8 −18·5*	+10 +69*	−50	+85
11	+ 6·7	+13	−24	+25	−19	− 8·8	—	—	−24	+23
12	+ 9·0	−24	−49	+26	−17	+11	+ 5·9	+50	−28	—
13	+14·6	+19·5	−19·5	+77	−17·5	+17·5	—	—	−46	+100
Average per cent. change	0	+11	−41	+51	− 8	+16	− 2 −25	+16 +49*	−32	+49

* Large dose (2 g. 4-hourly). † 7½ gr. t.d.s. 2 days. 15 gr. t.d.s. 1 day.

significant if there was an average fall of at least 15 per cent. in the level of the plasma uric acid (after administration) and an average rise of at least 30 per cent. in the urinary excretion of uric acid (during administration).

Results

The following is a summary of the effects of each preparation:

(1) Colchicine.—This was given in tablet form orally in a dose of 1/120 gr. three times daily for 3 days to twelve patients. In only four cases (4, 6, 7, 8) was there any fall in the level of the P.U.A., the fall varying from 9·6 to 27·5 per cent. (average 21·4 per cent.); in three of these four cases the fall was greater than 15 per cent. In seven cases (2, 3, 5, 8, 9, 11, 13) there was a rise in the U.U.A., the figure varying from 13 to 70 per cent. (average 29 per cent.); in only two of these cases (3 and 5) was the rise more than 30 per cent. In only one case (8) was there a concomitant fall in the P.U.A. and rise in the U.U.A., the former being 26 per cent. and the latter 25 per cent.

Three patients (Cases 2, 4, and 8) developed gouty pains—in one case this amounted to an acute attack of gout—on the day before receiving the course of colchicine. The pains settled down rapidly during colchicine administration.

(2) Sodium Salicylate.—This was given in mixture form in doses of 30 gr. (2 g.), together with 15 gr. (1·0 g.) sodium bicarbonate four times daily for 3 days to twelve patients. In every case there was a fall in the level of the P.U.A. varying from 12 to 70 per cent. (average 42·5 per cent.); in eleven of the cases the fall was

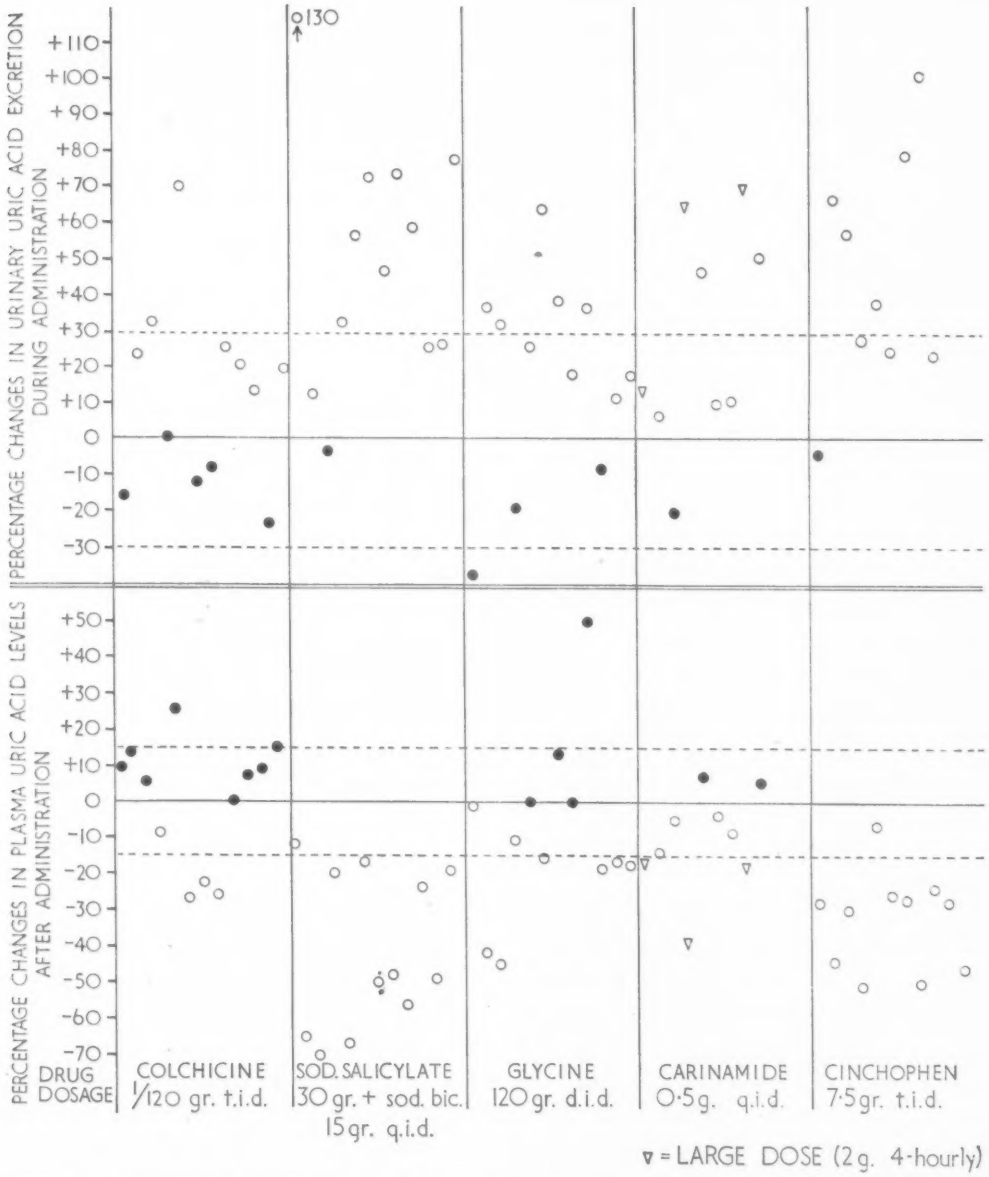

FIGURE.—Diagrammatic representation of percentage changes in plasma uric acid and urinary uric acid after and during administration of five different drugs.

greater than 15 per cent. In eleven of the twelve cases there was a rise in the U.U.A., the increase varying from 12 to 130 per cent. (average 55 per cent.), and in eight of these the rise was more than 30 per cent. In the one case in which there was a fall in the U.U.A., the fall in the P.U.A. was the maximum noted (70 per cent.).

Four patients (2, 3, 8, 10) developed either an acute attack of gout or milder gouty pains within 72 hours after completing the course of sodium salicylate. This happened in spite of the fact that, at the time that the pains began, the P.U.A. was unusually low, varying from 2·4 mg. to 4·4 mg. per cent.

(3) Glycine.—This was given orally in doses of 120 gr. (8 g.) twice daily for 3 days to twelve patients. In eight cases there was a fall in the level of the P.U.A., the figure varying from 1·5 to 45 per cent. (average 21 per cent.); in six of the eight cases the fall was greater than 15 per cent. In nine cases there was a rise of U.U.A., the figure varying from 11 to 63 per cent. (average 30·7 per cent.); in five of the nine cases the rise was more than 30 per cent. Altogether there were only five cases (2, 3, 7, 12, 13) in which there was a concomitant fall in the P.U.A. and rise in the U.U.A.

In two patients (3 and 5) an attack of gout developed within a day of beginning the course of glycine, and in one patient (11) gouty pains occurred on the day after the course of glycine was completed.

(4) Carinamide.—This drug, phenyl methane (4^1 carboxyl) sulphonanilide, $\langle\!\rangle\ CH_2 . SO_2 . NH \langle\!\rangle\ COOH$, was given in cachets or tablets orally. In six patients the dose was 0·5 g. four times daily, and in three (1, 6, 10) 2 g. four-hourly for 3 days. Two of these three (6, 10) had previously received the smaller dose. In four of the six patients receiving the small dose, there was a fall in the P.U.A. ranging from 4·3 to 14·5 per cent. (average 8·3 per cent.), in five there was a rise in the U.U.A. varying from 6·2 to 50 per cent. (average 24·3 per cent.); in only two of these (7 and 12) was the rise greater than 30 per cent. In all three patients receiving the larger dose there was a concomitant fall in the P.U.A. and rise in the U.U.A., the former varying from 17 to 39 per cent. (average 28 per cent.), and the latter from 13 to 69 per cent. (average 48·6 per cent.); in all three the fall in the P.U.A. was greater than 15 per cent., and in two of them the rise in the U.U.A. was above 30 per cent.

One patient developed an acute attack of gout within two days of completing the course of carinamide.

(5) Cinchophen.—This was given orally in doses of 7½ gr. (0·5 g.) three times daily for 3 days to nine patients, and in doses of 7½ gr. (0·5 g.) three times daily for two days, and 15 gr. (1·0 g.) three times daily for a third day, to two patients (6 and 8). In all eleven cases there was a fall in the level of the P.U.A. varying from 6·8 to 51 per cent. (average 32·8 per cent.); in ten of them the fall was greater than 15 per cent. In nine of the eleven cases, there was a rise in the U.U.A., varying from 23 to 100 per cent. (average 55 per cent.); in six of these nine the rise was more than 30 per cent. In one case the level of the U.U.A. was not estimated, and in the other it fell by 5·1 per cent.

(6) Probenecid ("Benemid").—This drug, *p*-(di-*n*-propylsulphamyl)-benzoic

acid, $(C_3H_7)_2$ N.SO_2 <⟶> COOH, was given orally in a dose of 0·5 g. four times daily to eight additional patients (not included in Table or Figure). In all cases there was a fall in the level of P.U.A., varying from 18 to 62 per cent. (average 40 per cent.), and a rise in the level of U.U.A., varying from 19 to 120 per cent. (average 55 per cent.). In all cases the fall in P.U.A. was more than 15 per cent., and in five out of the eight, the rise in U.U.A. was more than 30 per cent.

Two patients (one a female suffering from tophaceous gout) developed an acute attack of gout 2 to 3 days after completing the course, when the P.U.A. was comparatively low. In the case of the female, this was the first attack she had had for many years. Two other patients developed an attack of gout on the second day of the three-day course of Benemid; in both cases the P.U.A. was also comparatively low, one being the lowest ever recorded in a total of fourteen estimations, eight of them on consecutive days.

Conclusions

Observations were made on the effect of a series of drugs on the plasma uric acid and daily excretion of urinary uric acid in thirteen classical cases of gout during the interval phase. Owing to normal variations in uric acid levels, a fall of less than 15 per cent. in the plasma uric acid, and a rise of less than 30 per cent. in the urinary excretion of uric acid was considered of no significance. Taking into account this normal variation, the results were as follows:

(*a*) *Colchicine*, 1/120 gr. three times daily—although this drug was clinically effective, in only three out of twelve cases was there a fall in the P.U.A., and in only two out of twelve an increase of the U.U.A.

(*b*) *Sodium Salicylate*, 30 gr. (2·0 g.) four times daily—in eleven out of twelve cases there was a fall in the P.U.A. and in eight an increase in the U.U.A.

(*c*) *Glycine*, 120 gr. twice daily—in six out of twelve cases there was a fall in the P.U.A. and in five a rise in the U.U.A.

(*d*) *Carinamide*, 0·5 g. four-hourly—no patient showed a fall in the P.U.A., but two out of six showed an increase in the U.U.A. On a dosage of 2·0 g. four-hourly, however, three out of three cases showed a fall in the P.U.A. and two out of three a rise in the U.U.A.

(*e*) *Cinchophen*, 7·5 gr. (0·5 g.) three times daily—ten out of eleven showed a fall in the P.U.A., and six out of eleven showed a fall in the U.U.A.

(*f*) *Probenecid*, 0·5 g. four times daily—eight cases all showed a fall in the P.U.A. and a rise in the U.U.A.

The average percentage decreases in plasma uric acid and increases in urinary uric acid were:

Drug	Decrease %	Increase %
Colchicine ..	0	+11
Sodium Salicylate	−41	+51
Glycine	− 8	+16
Carinamide ..	−25	+49
Cinchophen ..	−32	+49
Probenecid ..	−40	+55

Although from the clinical point of view we are of the opinion that colchicine is probably the most important single therapeutic weapon in gout, both in the

acute and interval phase, these figures show that salicylates, cinchophen and, in the larger dosage, carinamide and probenecid are the only drugs which have any significant effect on the plasma and urinary uric acid in the dosage usually employed.

Summary

The effect of six drugs on the plasma and urinary uric acid in gout has been investigated. Salicylates, cinchophen, large doses of carinamide, and probenecid appeared to produce a significant result, while colchicine and glycine were without this effect.

We should like to thank Dr. Pearson for assistance in the laboratory and the Empire Rheumatism Council for financial help.

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Goutte: Observations sur les Effets de Divers Médicaments sur l'Acide Urique du Plasma et de l'Urine

Résumé

On a étudié l'effet de six médicaments sur l'acide urique du plasma et de l'urine dans la goutte. Les salicylates, la cinchophène, de fortes doses de carinamide, et la probénécide semblaient produire un résultat significatif, tandis que la colchicine et la glycine restaient sans effet.

Gota: Observaciones sobre los Efectos de Varios Medicamentos sobre el Ácido Úrico del Plasma y de la Orina

Sumario

Se han investigado los efectos de seis medicamentos sobre el ácido úrico del plasma y de la orina en casos de gota. Salicilatos, " cinchophen ", fuertes dosis de carinamida, y " probenecid " parecían producir un resultado significativo mientras que la colchicina y la glicina fueron carentes de este efecto.

COMPARATIVE THERAPEUTIC VALUE OF MASSAGE WITH "ADRENALINE CREAM" AND WITH ANOTHER CREAM IN CONDITIONS ASSOCIATED WITH DEEP PAIN

The therapeutic trial described below was designed at the request of the research subcommittee of the Empire Rheumatism Council to evaluate the specific efficiency of a proprietary product, widely advertised in the lay press as a cure for rheumatism, etc., and claimed by Moss (1949) to be of very great value in fibrositis.

The specific question asked was whether there was any difference between "Adrenaline Cream" and a similar cream not containing adrenaline, such as Howell (1950) had noted. The latter author obtained relief "within a few minutes" which "lasted for several hours at least". In 83 out of ninety patients with chronic fibrositis usually secondary to rheumatoid arthritis or osteo-arthritis, the inunction of adrenaline cream by deep massage relieved the pain for from 10 minutes to 5 days. "The usual duration of freedom from pain was 12 hours." Similar results were obtained with other medicated creams containing ephedrine or belladonna, but "a blank control cream gave only 2 or 3 hours relief in most of the twenty patients".

Procedure

The experiment was carried out at the following ten rheumatism centres in England and Scotland: Royal Infirmary, Aberdeen (Dr. Logie Bain), University College Hospital, London (Dr. H. A. Burt), West London Hospital (Dr. W. S. C. Copeman), Northern General Hospital, Edinburgh (Dr. J. J. R. Duthie), Royal Free Hospital, London (Dr. E. Fletcher), Middlesex Hospital, London (Dr. F. D. Howitt), Royal Infirmary, Manchester (Dr. J. H. Kellgren), Royal National Hospital for Rheumatic Diseases, Bath (Dr. G. D. Kersley), and the Canadian Red Cross Memorial Hospital, Taplow, and British Postgraduate Medical School, London (Dr. E. G. L. Bywaters). Dr. E. Lewis-Faning gave advice and made useful suggestions regarding the planning of the trial and its statistical analysis.

Material.—"Adrenaline Cream" was used as supplied by the makers (Messrs. Howard Lloyd of Leicester). Comparison was made with the effects of a control cream (similar but not containing adrenaline), as used by Howell (1950):

Emulsifying wax ..	20 parts
Wool fat	10 parts
Chlorocresol ..	0·05 parts
Water	100 parts

The cost of these materials is 1*d.* per oz.; the cost of the "adrenaline cream" is 3*s.* 9*d.* for a 2-oz. tin, which includes the cost of mixing, packaging, marketing, etc.

Cases.—Patients were selected with bilateral back pain or pain in two non-symmetrical positions in the body due to "fibrositis" (i.e. deep pain referred to muscle): the presence of degenerative joint disease or rheumatoid arthritis did not exclude the case.

Method.—The two creams were labelled by the pharmacist "A" and "B", so that although slight differences were noted in the two creams by the investigators, they did not know beforehand which was which. Some observers noted that the adrenaline cream darkened slightly on exposure, or that one of the creams rubbed in slightly differently. All the massage in each centre was done by the same person.

The two creams were each massaged into one of the two sites for five minutes, and the effects assessed before treatment, and 5 min., 30 min., and one week after starting treatment. At the second attendance (one week from the first inunction) the sites of inunction of the creams were reversed and the same procedure carried out.

Evaluation of Effects.—Subjective assessment of pain was made by enquiring how bad the pain was before and at each of the three intervals afterwards. It was graded 0, 1, 2 (none, mild, severe). Objective tenderness was tested by manual pressure, before and at each of the three intervals afterwards (graded 0, 1, and 2 as above). The retrospective duration of relief, if any, was enquired into at the two weekly return visits.

Results

It will be seen that improvement, partial (from Grade 2 to Grade 1) or complete (from Grade 1 or 2 to 0), occurred in one quarter of the trials (Table I, opposite), irrespective of whether comparison was made

(*a*) between the two creams,
(*b*) between the two sites,
(*c*) between the subjective and the objective assessment,
(*d*) between the first trial and the replication,
(*e*) between the 5-minute and the 30-minute assessment (Table II below).

The greatest difference (Table II) was between the 5-minute and the 30-minute assessment, but this was not large and should be ascribed to the psychological response on the part of the patient to a repetition of the pain enquiry.

TABLE II
NUMBER IMPROVED OUT OF POSSIBLE IMPROVEMENTS

First Trial	Second Trial	Subjective	Objective	Adrenaline	Control	5 min.	30 min.	One Side	Other Side
4/36	12/31	4/36	9/38	4/36	7/38	4/36	12/36	4/36	12/31
9/38	6/36	12/31	6/36	9/38	7/38	9/38	14/38	9/38	6/36
7/38	10/30	10/30	8/37	12/31	10/30	12/31	14/31	10/30	7/38
7/38	8/37	7/38	7/38	6/36	8/37	6/36	10/36	8/37	7/38
12/36	14/31	12/36	14/38	12/36	10/38	7/38	10/38	12/36	14/31
14/38	10/36	14/31	10/36	14/38	10/38	7/38	10/38	14/38	10/36
10/38	11/30	11/30	9/37	14/31	11/30	10/30	11/30	11/30	10/38
10/38	9/37	10/38	10/38	10/36	9/37	8/37	9/37	9/37	10/38
73/300	80/268	80/270	73/298	81/282	72/286	63/284	90/284	77/282	76/286
24%	30%	29%	25%	29%	25%	22%	31%	27%	27%

TABLE I

Effect on Patient				Improvement		Worse	No Change	No Pain Initially
				Partial	Complete			
Assessment after 5 min.	ADRENALINE	First trial	Subjective	1	3	1	31	3
			Objective	8	1	1	28	1
		Replication	Subjective	2	10	3	16	8
			Objective	0	6	3	27	3
	CONTROL	First trial	Subjective	2	5	0	31	1
			Objective	6	1	2	29	1
		Replication	Subjective	1	9	(1)(*a*)	20	9
			Objective	4	4	2	27	2
Assessment after 30 min.	ADRENALINE	First trial	Subjective	6	6	(3)(*a*)	22	3
			Objective	10	4	2	22	1
		Replication	Subjective	3	11	0	17	8
			Objective	3	7	1	25	3
	CONTROL	First trial	Subjective	4	6	1	27	1
			Objective	9	1	3	25	1
		Replication	Subjective	3	8	(3)(*b*)	18	9
			Objective	5	4	1	27	2
Total		Adrenaline		33	48(81)	14(*a*)	188	30
		Control		34	38(72)	13(*c*)	204	26

(*a*) includes one with no pain initially.
(*b*) „ two „ „ „ „
(*c*) „ three „ „ „ „

The only certain facts which emerged were these:

(1) Partial improvement occurred more frequently on the first objective assessment (at both 5 and 30 minutes and with both control and adrenaline cream) than on the replication (Table I).

(2) Complete improvement occurred more frequently subjectively than objectively and more often on the replication than on the first assessment (Table I).

(3) The pain had disappeared completely in several patients by the time of the replication (one week), a fact for which due allowance is made. In some, partial disappearance at this time (subjective only) had occurred.

TABLE III

ANALYSIS OF REPRODUCIBILITY

Assessments	Subjective		Objective	
	Adrenaline	Control	Adrenaline	Control
(*a*) AFTER 5 MIN.				
Agreement	18	21	24	22
Both improved	3	2	3	2
Both no change	15	19	21	20
Both worse	0	0	0	0
Disagreement	11	9	12	15
Worse and no change	4	1	3	4
Better and no change	7	8	8	11
Better and worse	0	0	1	0
(*b*) AFTER 30 MIN.				
Agreement	16	17	24	20
Both improved	5	2	7	3
Both no change	11	14	17	17
Both worse	0	1	0	0
Disagreement	14	14	12	17
Worse and no change	1	1	2	4
Better and no change	12	12	9	13
Better and worse	1	1	1	0

(4) Agreement between the first trial and the replication (Table III) was more common than disagreement, both for subjective and for objective assessments, and especially at 5 minutes (85 to 47); but this was chiefly accounted for by those cases who showed no change. Disagreement was more common than agreement, if we include in the latter only cases which showed improvement both at the first testing and also at the replication (47 to 10 at 5 minutes, and 57 to 18 at 30 minutes).

(5) Some observers consistently scored " improvement ", " no change ", or " worse " more often than the rest. Comparing four centres who analysed five to eight cases each (Table IV), the percentage improvement ranges between 6, 17, 37, and 43, with " worsening " in 12, 0, 5, and 4 per cent. respectively. This could be due to pessimistic and sceptical patients in the first centre, and expectant and hopeful ones in the others, which seems more probably due to psychological conditioning in the centre than to natural selection. It is not thought that standards of assessment varied much, since there is in general good agreement between subjective and objective responses.

TABLE IV

Centre	No. of Cases	Improvement	Worsening	Total	Per cent.	
					Improved	Worse
A	6	32	4	87	37	4·6
B	5	12	0	72	17	0
D	6	5	10	86	5·8	11·6
H	8	47	4	110	43	3·6

(6) Comparing the results for "adrenaline cream" with those of the control cream, no significant difference was found for either the subjective evaluation (additive $\chi^2=0\cdot675$, $n=4$, p between $0\cdot95$ and $0\cdot98$), the objective evaluation (additive $\chi^2=0\cdot690$, $n=4$, p between $0\cdot95$ and $0\cdot98$), or both together ($\chi^2=1\cdot365$, $n=8$, and $p>0\cdot99$). Thus we are unable to demonstrate a significant difference using the above criteria between the proportion improved on adrenaline cream and those improved on the control cream.

(7) The retrospective enquiry about the duration of relief from pain (Table V) showed no significant difference between those treated with control and those treated with adrenaline cream ($\chi^2=0\cdot25$).

TABLE V
DURATION OF RELIEF

Duration of Relief (hrs)	Adrenaline		Control Cream	
	1st Trial	Replication	1st Trial	Replication
24+	14	19	13	19
0-23	10	3	7	4
None	15	14	19	13
Total Cases ..	39	36	39	36
Total with Relief	46		43	
Total with no Relief ..	29		32	

No significant difference is demonstrated. ($\chi^2=0\cdot25$.)

It may be alleged that adrenaline is unstable and rapidly disintegrates. No special precautions were taken to prevent this, but it seems likely that a good reproduction of the conditions seen in daily practice was achieved.

Conclusion

We conclude that there is little difference between the effects of the proprietary preparation costing 3*s.* 9*d.* a tin and a similar unmedicated cream, the basic ingredients of which cost 2*d.* for the same amount, and that what difference we have demonstrated by this method of testing is too small to warrant the assumption of a significant difference between the two products.

Summary

(1) A trial was planned at the request of the Empire Rheumatism Council to evaluate the therapeutic efficiency of a cream containing adrenaline which was claimed to relieve the pain of "fibrositis" when rubbed into the painful area.

(2) Experiments were carried out at ten rheumatism clinics. A total of 39 patients with pain in two sites were massaged with adrenaline cream at one site, and with a control cream (of similar composition but excluding adrenaline) at the other. A week later the procedure was repeated with the sites reversed. The

investigators were unaware which cream was which, and the massage was all done by the same person at each centre. The degree of pain was assessed subjectively and objectively, before treatment, and 5 min., 30 min., and one week after treatment.

(3) Improvement, partial or complete, occurred in 29 per cent. of trials with adrenaline cream, and in 25 per cent. of controls.

(4) The difference between the results with adrenaline cream and those with the control cream was too small to be significant; it was concluded, therefore, that there was little difference between the effects of the two creams when tested by this method.

Acknowledgements are due to the staff of the ten centres centres listed above who carried out the investigation and provided the data on which this analysis is based.

E. G. L. BYWATERS, F.R.C.P.
Chairman, Research Sub-Committee of the Empire Rheumatism Council

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Comparaison de la Valeur Thérapeutique des Frictions avec la " Crème à l'Adrénaline " et des Frictions avec une autre Crème dans des Affections accompagnées de Douleur Profonde

RÉSUMÉ

(1) A la demande de l'*Empire Rheumatism Council* des recherches furent entreprises afin de déterminer l'efficacité thérapeutique d'une crème contenant de l'adrénaline qui, appliquée en friction à la surface endolorie, atténuerait—prétendait-on—la douleur de la " fibrosite ".

(2) Des recherches furent effectuées dans dix cliniques rhumatologiques. En tout, 39 malades se plaignant de douleur en deux endroits différents durent frictionnés avec la crème adrénalinée à un endroit, et avec la crème-étalon (de composition similaire, mais sans adrénaline) à l'autre. Une semaine plus tard on répéta le procédé en inversant l'endroit de l'application. Les expérimentateurs ignoraient l'identité précise des crèmes, et dans chaque centre toutes les frictions furent effectuées par la même personne. Le degré de la douleur fut déterminé subjectivement et objectivement avant le traitement, et 5 minutes, 30 minutes, et une semaine après le traitement.

(3) Une amélioration, partielle ou totale, se produisit dans 29% des applications de la crème adrénalinée et dans 25% des applications de la crème-étalon.

(4) La différence entre les résultats acquis avec la crème adrénalinée et ceux obtenus avec l'étalon était trop petite pour etre significative. On en conclut, par conséquent, qu'il y avait très peu de différence entre les deux crèmes comparées au moyen de la méthode décrite.

Comparación del Valor Terapéutico de Masaje con " Crema de Adrenalina " y con otra Crema en Afecciones acompañadas de Dolor Profundo

SUMARIO

(1) A solicitud del *Empire Rheumatism Council* investigaciones fueron emprendidas para determinar la eficacia terapéutica de una crema conteniendo adrenalina que pretendidamente calmaba el dolor de la " fibrositis " al frotar con ella la zona endolorida.

(2) Investigaciones fueron efectuadas en diez clínicas reumatológicas. En total, 39 enfermos con dolor en dos sitios diferentes fueron friccionados con crema adrenalinada en un sitio, y con una crema de control (de composición similar, pero sin adrenalina) en el otro. Una semana más tarde el procedimiento fué repetido, invirtiendo los sitios de aplicación. Los experimentadores ignoraban la identidad precisa de las cremas, y en cada centro el masaje era practicado por una misma persona. El grado de dolor fué determinado subjetiva y objetivamente antes del tratamiento, y 5 minutos, 30 minutos, así como una semana después del mismo.

(3) Mejoría, parcial o completa, ocurrió en 29% de los experimentos con crema de adrenalina, y en 25% de los experimentos de control.

(4) La diferencia entre los resultados obtenidos con crema de adrenalina y con la de control fué demasiado pequeña para ser significante. Se concluye, por lo tanto, que era poca la diferencia entre las dos cremas, cuando comparadas por este método.

ROYAL COLLEGE OF PHYSICIANS

REPORT OF THE COMMITTEE ON CHRONIC RHEUMATIC DISEASES

The Committee appointed in 1950 has met on five occasions, and the following report was passed by the Fellows of the College at the Comitia on July 26, 1951.

Definition.—A precise definition of the chronic rheumatic diseases is difficult, but for practical purposes the field under consideration should include rheumatoid arthritis, osteo-arthritis, spondylitis, gout, and the various forms of non-articular rheumatism, together with the differential diagnosis of these from other conditions which may simulate them.

Introduction.—These diseases are of great importance for economic reasons owing to the large number of man-hours they cause to be lost each year, and equally for humanitarian and medical reasons because of the extent to which they cripple the patient and disrupt family life. Until recently, however, they have received scant attention in the way of organized treatment, teaching, or research.

Early specialization in this field, and the excessive multiplication of posts devoted exclusively to chronic rheumatic diseases leading to further unnecessary fragmentation of general medicine are to be deprecated. However, within the scope of general medicine, the importance of this group of diseases deserves greater recognition for their effective control. In this connection, gastro-enterology, cardiology, and neurology may be cited as examples of branches of medicine requiring varying degrees of special training, yet remaining as part of general medicine.

Thus the chronic rheumatic diseases should not generally be a whole-time specialty, but should constitute a special interest within general medicine; alternatively, after appropriate training in general medicine, this specialty could be combined with physical medicine or orthopaedics.

Study in this field should not be allowed to become an easy route to consultant status, and it is recommended that a special diploma should not be established.

An adequate background of general medicine is essential for the diagnosis and treatment of the chronic rheumatic diseases. In addition, however, some special knowledge of orthopaedics, physical medicine, and endocrinology is necessary.

Establishment of Special Centres

The best method of advancing the study of chronic rheumatic diseases is by the development of special centres throughout the country to the number of approximately one per region; this might include special centres already in existence, some of which might need expansion. These centres should be primarily concerned with research and teaching, but would also influence the general standard of treatment. They should be in close liaison with the medical department of a general hospital, and should be linked with university teaching and research departments, including those of the basic sciences. They should be the joint responsibility of the University, the Teaching Hospital, and the Regional Hospital Board. Each centre should be in the charge of a Physician with good general medical training and special experience in this field, and the junior staff should consist of house physicians and registrars, preferably in the latter part of their training.

While it is recognized that the recommended special centres would mean special allocation of beds for the treatment of chronic rheumatic diseases, it is felt that the aggregation of chronic rheumatic patients in these beds, as well as setting free beds in general wards, might decrease the average duration of stay in hospital by reason of the special treatment available.

Functions of Centres

Research.—Research projects would be pursued under the direction of the Physician-in-charge, with the co-operation of the appropriate department of the associated Hospital and University.

Teaching.

(*a*) Special training for those physicians who wish to adopt this specialty as their main work.
(*b*) Training courses for general physicians, specialists in physical medicine, and orthopaedic surgeons who wish to be seconded to these centres for this purpose.
(*c*) Short courses for general practitioners.

(*d*) Undergraduate teaching in co-operation with the medical department of the associated medical school.

In the past the chronic rheumatic diseases have often received inadequate attention in undergraduate education. A regular series of lecture-demonstrations should form a part of the final year of clinical study and that, in some cases, a short period of clerking in the wards of the rheumatic unit would be of considerable value to the student, in view of the high incidence of these diseases in general practice. An improvement in undergraduate instruction in this subject would contribute to an improvement in the treatment of chronic rheumatic disease.

Training.—It is desirable that a physician who aims at obtaining charge of such a special centre should have held the appointment of house physician for 6 months, either during his year of provisional registration or subsequently, and that he should receive the following *minimal* full-time training:

2 years in a registrar or comparable post in general medicine
2 years in a registrar or comparable post in a rheumatic centre
6 months' training in orthopaedics
6 months' training in physical medicine
1 further year in *one* of the following:

(*a*) study abroad,
(*b*) research,
(*c*) further experience in general medicine and its branches, endocrinology, neurology, physical medicine, or orthopaedics.

The minimal training after completion of house officer duties is thus envisaged as 6 years, a period comparable with that of other branches of medicine. The final year leaves a large margin of individual choice.

The M.R.C.P.(Lond.), or an accepted equivalent, should normally be taken before special study of the chronic rheumatic diseases is commenced, but it is recognized that in exceptional circumstances it may be permissible for the trainee to sit for his higher medical qualification during his period of special training.

Conclusions

(1) The organization of the treatment of the chronic rheumatic diseases should receive special consideration.

(2) Special centres for chronic rheumatic diseases should be developed throughout the country, approximately one per region.

(3) These centres should be primarily concerned with research and teaching.

(4) There should be close liaison between these centres and a general hospital, and university teaching and research departments, including those of the basic sciences.

(5) Each centre should be in the charge of a Physician with good general training and special experience in this field. He should have a higher qualification in medicine and should have a staff of house physicians and registrars.

(6) The minimal training of a Physician-in-charge of such a centre should be 6 months as house physician, either during his year of provisional registration or subsequently, 2 years in a registrar or comparable post in general medicine, and a further 4 years' special training.

MEMBERS OF THE COMMITTEE

Dr. W. Russell Brain (*President*).
Dr. Anthony Feiling.
Sir John Conybeare.
Dr. Frank Howitt.
Dr. W. S. C. Copeman.
Prof. W. G. Barnard.
Dr. E. T. Conybeare.
Prof. L. S. P. Davidson.
Dr. G. D. Kersley (*Secretary*).
Sir Ernest Rock Carling.
Dr. E. G. L. Bywaters.
Dr. F. S. Cooksey.
Mr. H. Osmond-Clarke.
Sir Harold Boldero.

BRITISH BRANCH OF THE EUROPEAN LEAGUE AGAINST RHEUMATISM

ANNUAL GENERAL MEETING, 1951

The Annual General Meeting of the British Branch of the Ligue Européenne contre le Rhumatisme was held at the Arthur Stanley Institute (Middlesex Hospital) on July 6, with the President, Dr. W. S. C. Copeman, in the Chair. The Hon. Treasurer presented the accounts; these showed a small credit balance, but he pointed out the need for more members.

The Chairman then presented his annual report and drew attention to the link with the Ligue Européenne, to which they subscribed, the hospitality received from the Heberden Society, and the invitation to members to visit clinics and partake of the facilities of the Empire Rheumatism Council's autumn tour of British rheumatic centres.

The following officers were re-elected for the next two years:

Dr. W. S. C. Copeman (*President*)
Dr. G. D. Kersley (*Hon. Treasurer*)
Dr. Oswald Savage (*Hon. Secretary*).

After the general meeting, five clinical papers were given, followed by discussions.

DR. BERNARD SCHLESINGER gave the opening paper on Still's disease with special reference to the haemopoietic system. He stressed the pre-arthritic stage with fever, leucocytosis, and sometimes a macular rash as prominent features, followed later, especially in severe cases, by a leucopenic phase. Bone-marrow examination did not reflect the circulating blood picture. This paper will be published in a future issue of this Journal.

DR. L. J. BARFORD gave an account of the use of " Collosol " Manganese 2·5 per cent. solution injected intramuscularly in a series of " rheumatic " cases. Favourable results were often seen within a few days in cases of osteo-arthritic knees and in capsulitis of the shoulder.

DR. H. WARREN CROWE described the use of Trafuril (Ciba), a nicotinic acid derivative, which on inunction as a cream or being painted on as a tincture had a good rubefacient and anaesthetic action, somewhat similar to histamine ionization. Given by injection at the same time as gold, it had, he thought, prevented the stiffness reaction so often felt on the second day after aurotherapy.

DR. LOUIS MOSS spoke of the beneficial effects of adrenaline cream on trigger spots in fibrositis. He repeated the claims he has published elsewhere, but these were not substantiated by members of the audience, in the subsequent discussion.

DR. G. D. KERSLEY, in a provocative paper on the practical uses of cortisone and ACTH, said that as a research tool these hormones were of outstanding importance. In certain ophthalmic diseases they might save sight, and in other non-rheumatic conditions, such as burns and status asthmaticus, they might be invaluable. In rheumatic fever the condition was controlled but not cured, their effect being not unlike that of salicylates. In systemic lupus they might prolong life, in scleroderma they were often disappointing, in acute gout they might be of value. In treatment of pain in osteo-arthritis he had found them to produce no benefit. In cup arthroplasty they were worthy of trial.

It was, however, in rheumatoid arthritis that their value was in most debate, and he suggested the following uses:

(1) to cover some temporary or removable cause in acute cases.
(2) to cover episodes such as influenza, shock, etc., in quiescent and slight rheumatoid arthritis.
(3) to cover manipulation of joints in a 3-day course of 100-200 mg. cortisone/24 hrs.
(4) to treat cases that flare up with surgery.
(5) to assist mild cases that can be got back to work and can be kept on the active list with care and encouragement.

Dangers were listed as:

(1) severe relapse or adrenal failure on sudden cessation of treatment;
(2) psychological effect of relapse;
(3) temporary manic effect in those of unsound mental background;
(4) possible spread of infection (not yet decided);
(5) delayed healing of wounds;
(6) temporary Cushing's syndrome;
(7) tendency to thrombosis;
(8) deterioration of a diabetic state.

A knowledge of the clinical effects of cortisone and ACTH was more important for their successful use than were extensive laboratory facilities. In conclusion three pleas were made:

(*a*) that cortisone should never take the place of any other form of treatment that might be indicated on general grounds, but should be used in addition to these measures;
(*b*) that while on cortisone the patient's activities should still be controlled—he must recharge his batteries, but not turn on the headlights till they were completely charged;
(*c*) that dosage should be very gradually decreased when treatment is to be discontinued.

URUGUAYAN LEAGUE AGAINST RHEUMATISM

OFFICERS, 1951-2

The following officers have been re-elected for the year 1951-52:

President:	Dr. Pedro M. Gaudiano
Vice-President:	Dr. Pedro Rivero Arrate
Secretary:	Dr. Benito Barrós
Assistant Secretary:	Dr. Luis P. Gómez
Treasurer:	Dr. Felipe Barrabino
Committee Members:	Dr. Antonio Fisano
	Dr. Washington Ayala
	Dr. Pablo Scremini
	Dr. Raúl Cioli

SOCIETÀ ITALIANA PER LO STUDIO DEL REUMATISMO

ACQUI PRIZE FOR RHEUMATOLOGY

An international competition for unpublished work on the rheumatic diseases was held at Acqui in June under the patronage of the Italian Society for the Study of Rheumatism.

The judges were Dr. W. S. C. Copeman, President of the European League against Rheumatism, Professor Martin (Geneva), Dr. F. Françon, Vice-President of the French Branch of the League, and Professors Villa (Milan), Sabatini (Genoa), and Quaglia (Acqui). The prize of one and a half million lire was divided amongst three groups of workers: the first award was to Professor T. Lucherini and Drs Cecchi, Cervini, Via, Mattoli, and Volpicelli of Rome, for a volume on the semiology of articular diseases; the second was to Professor A. Robecchi of Turin, for his work on periarthritis of the shoulder joint; the third was to Drs Ballabio, Cavallero, and Sala of Milan, who wrote on the biological and clinical effects of the adrenal corticoids and their effects in the rheumatic diseases.

At the meeting it was decided that the Society should apply for affiliation to the European League as representing the Italian Branch, and Professor Sabatini of Genoa was elected President.

BOOK REVIEWS

Endocrine Diagnosis. By H. Ucko. 1951. Staples Press, London. Pp. 513. 42*s*.

Recent researches on the effects of the anterior pituitary gland and the hormones of the suprarenal cortex in collagen diseases have aroused a widespread interest shared by the general physician and the endocrine specialist alike. In recent years interest has moved from the classical description of the known endocrine diseases to a study of the part played by the endocrine glands in health and disease and the possible endocrine aetiology of diseases with doubtful or unknown aetiology.

Dr. Ucko has attempted to co-ordinate our present knowledge of the endocrine diseases and their diagnosis with a systematic discussion of the involvement of endocrine factors in the physiology and pathology of the organism as a whole and in diseases which are not primarily of endocrine origin. He also discusses endocrine influences, known and probable, on the various organs and structures of the body. The first part of the book, about 300 pages, is devoted to clinical findings and the endocrine influences on different body structures, and on the mechanism of the major events of life. Signs, symptoms, and differential diagnosis are set out in detail, and, where possible, arranged in tabular form. This system of regional clinical findings is an excellent one and saves time for the busy physician in search of a particular sign or syndrome.

The second part of the book deals with the physiology and disorders of the endocrine glands. A separate chapter is devoted to each gland, and the modern laboratory tests used as an aid to diagnosis are included.

Certain sections, particularly those dealing with the adrenal cortex and the anterior pituitary gland might with advantage be expanded. The illustrations are excellently reproduced, and photographs of typical cases clearly bring out many points in the text, so that we hope that they will be more numerous in the next edition. Finally, there is an excellent bibliography.

G. N. MYERS.

Recent Advances in Physical Medicine. Edited by Francis Bach, M.A., D.M.(Oxon.), D.Phys.Med. J. and A. Churchill, London. 93 illus. 27*s*. 6*d*.

The division of Medicine into specialties is one of the problems of the times, even cardiologists have their misgivings when they find themselves breeding a series of specialists for each of the three standard and most of the unipolar leads.

The comparatively new specialty of physical medicine belongs properly to a somewhat older hierarchy than that which relates to particular parts or organs of the body. Just as the specialties of radiology and pathology depend upon certain diagnostic techniques involving more capital equipment than can be carried in a top hat, so physical medicine is a specialty depending ultimately upon a particular therapeutic technique and apparatus: it is paralleled by surgery—one of the oldest subdivisions in medicine. It is a little surprising, when the physicians called the use of physic "iatrochemical medicine", that the surgeons did not call themselves "iatrophysical specialists", since surgery is the application to medicine of the mechanical physics which guide the carpenter and the plumber (not forgetting the plumber's mate). Since those days, the connotation of physical medicine as compared with chemical medicine has undergone considerable change, but its province is still the whole of medicine and in particular those diseases and conditions that can be ameliorated by the simpler physical devices, excluding the use of the knife and chisel, and stopping short at about 2,100 Ångström units on the spectrum, which then becomes the responsibility of the radiotherapist and of the atomic physicist.

In the old days, the techniques used in physiotherapy were limited to about five—ultra-violet light, heat in various forms, active and passive movements, massage, and electrical stimulation. The common habit of young house physicians of sending patients

for " some physiotherapy ", although never condoned and often condemned, might have been excused, especially since undergraduate instruction in this subject was and perhaps still is in many centres almost non-existent. But physiotherapy, or rather, physical medicine, may mean now anything from ultrasonic disintegration to psycho somatic rehabilitation. The conditions treated have correspondingly increased in number, although it is probably true that fibrositis, and what the Americans call " psychogenic rheumatism ", still make up the biggest single group in the average clinic. Thus it may be concluded that physical medicine is not just a new euphemism for physiotherapy.

These reflections have been aroused by a welcome and overdue addition on " Physical Medicine " to Churchill's " Recent Advances Series ". This volume, edited by Francis Bach, with 490 pages and 38 contributors, does not attempt to survey the whole field, but covers almost all the new ground which had been broken in the last 20 years, and emphasizes the crops with the most economically useful yield. These include Rehabilitation (A. R. Thompson and F. M. Ling), Re-employment and resettlement (John Arthur and Norah Hill), the School-child (E. H. Jebens), the Army (J. W. T. Patterson), and Industry (Katherine Williams). The editor contributes a characteristically thoughtful and thought-provoking preface on the scope and range of physical medicine, stressing the two main directions of advance, the development and use of instruments of precision, and the organization of rehabilitation. Throughout the book stress is laid on what is termed in several places the " holistic approach ".

The first four chapters deal with selected aspects of physics, anatomy, and physiology —including an exposition of the quantum concept and its relevance (Mendelssohn), a chapter on posture, and an account of the blood supply to the muscles (Blomfield). There then follows an excellent chapter on electrodiagnosis (Bauwens and Richardson), chapters on hydrotherapy, massage and manipulation, and home and occupational therapy. There is some repetition here and there, e.g. on electromyography, presumably difficult to avoid because of the collective authorship.

Guthrie Smith's chapter on remedial work and assisted exercises is a very valuable account of a field to which she has made a major contribution. It is surprising, however, that no mention is apparently made, here or elsewhere, of Delorme's careful work on progressive resistance exercises. As almost the only research prosecuted on the effects of exercise as carried out in physiotherapy departments, and as a model which might well be followed, this work deserves much wider recognition. Much mention is made of research in physical medicine (*vide* preface), but until the recent war it was almost unknown for the effects of any physiotherapeutic procedure to be adequately evaluated, most of the procedures being merely " thought to be useful ". The war stimulated several useful studies, such as that of the prevention of muscle atrophy by electrical stimulation, and some account of army research is given by Patterson in Chap. 25. By and large, however, the critical evaluation of methods of physical treatment in medicine is rare compared with the careful evaluation that what we might call " chemical " methods commonly entail.

The next section shows the application of physical medicine in various clinical fields e.g. rheumatism (Bach), orthopaedics (Girdlestone, Crisp, and Smart), and neuropsychiatry (Sandifer). The remaining sections deal with the organization of a department, public health aspects of rehabilitation and resettlement (particularly valuable), and the training in physical medicine of doctors (Kersley), and of physiotherapists (McAllister).

The book is well produced and there is a list of references (not always alphabetically arranged) to eleven of the 32 chapters. The reviewer particularly commends Fig. 60 for its refreshing realism, and most of the 93 illustrations are clear and helpful; Figs 43 and 44 may commend themselves to crossword addicts, though there are unfortunately neither clues in the text nor a solution in the back.

This will be found a useful book in many spheres besides that of physical medicine, and can be highly recommended to students and practitioners of that specialty.

E. G. L. BYWATERS.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the three abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, ABSTRACTS OF WORLD SURGERY, OBSTETRICS AND GYNAECOLOGY, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism: Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous): Sciatica: Gout: Non-Articular Rheumatism: General Pathology: ACTH, Cortisone, and other Steroids: Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section " ACTH, Cortisone, and other Steroids ", which appears for the second time in the present issue, includes abstracts and titles of articles dealing with steroid research, which although not directly concerned with the rheumatic diseases, may make an important contribution to knowledge of the scope and *modus operandi* of steroid therapy.

Acute Rheumatism

The Mechanism and Prevention of the Rheumatic State. BRADLEY, W. H. (1950). *Proc. roy. Soc. Med.*, **43**, 979. 2 figs, 31 refs.

The causal factors in rheumatic fever are an infective factor, probably *Streptococcus pyogenes*, acting on a genetically predisposed individual. The inherited factor determines an abnormal response to the infective agent. The abnormality consists in the production of a surfeit of antibody protein, excessive quantities of globulin both in the circulation and interstitially, and a resulting increase in blood volume. Evidence is reviewed bearing on the probability of these conclusions. The author recalls the commonly observed sequence of acute streptococcal sore throat, a lag period of about 2 weeks, then the first attack or a relapse of acute rheumatism; a rise in antistreptolysin O titre is also always observed. He refers to published genealogies suggesting that predisposition to acute rheumatism is transmitted by a recessive autosomal gene.

His own work, published in 1939, showed that at the beginning of rheumatic fever the apparent anaemia is a dilution phenomenon, essentially due to an absolute increase in the circulating plasma volume, and not to erythrocyte destruction. The serum was shown to have a high protein content, implying a great increase in total circulating protein. Rather more than twice the normal circulating globulin was present during active rheumatism, and the total circulating albumin tended to be somewhat below normal. The total circulating proteins remain at a high level during the height of rheumatic activity, and fall as the disease becomes quiescent. From this observation it seems improbable that the globulin mobilization is the antibody response to a specific rheumatic infection: for the rise begins before the onset of rheumatism, and does not increase during its course or persist in convalescence.

This leads the author to infer that the streptococcal infection merely fires off a chain of events, and has abated by the time that these events evoke the acute rheumatism. The new factor responsible for the rheumatic state is excess of antibody globulin, abnormal quantitatively and perhaps qualitatively because of the inherited predisposition. It is suggested that cortisone works through its function as an S hormone, affecting the conversion of protein into glycogen, that it has a bearing only on the inherited factor, and that the infective problem remains.

The following suggestions for the prevention of acute rheumatism are made. The children of rheumatic parents should be under the observation of public health officers. They should be housed in single bedrooms, employed in the fresh air and in small communities, nourished adequately, and educated to protect themselves from upper respiratory infection. Chemoprophylaxis should be applied at selected seasons. They should be advised never to marry a rheumatic subject, and to restrict their own families so as to be able to provide each child with a protected environment. *Kenneth Stone.*

Observations on the Epidemiology and Aetiology of Acute Rheumatic Fever. (Zur Epidemiologie und Atiologie des akuten Rheumatismus.) KUSTER, F. (1951). *Z. Kinderheilk.*, **69**, 161. 1 fig., bibl.

The well-defined clinical and histopathological picture of acute rheumatic fever has led some clinicians, in Germany notably Graff and Aschoff, to suppose that it is an infectious condition due to some specific, as yet unidentified, organism. In Britain and the U.S.A., where the disease is much commoner, epidemiological, bacteriological, and serological studies have led to a different view and one which in German literature is propounded by Klinge and Rössle. These observers hold that acute rheumatic fever is a response, probably allergic, to a non-specific acute streptococcal infection. The following findings of the author support this view: the incidence of rheumatic fever ran closely parallel with that of scarlet fever. Each " epidemic " of rheumatic fever (in institutions) was preceded by an epidemic of sore throats. Serological examination with various anti-streptococcal antigens showed that the antibody titre rose even higher in patients with rheumatic fever than in patients with streptococcal infections not followed by rheumatic fever. It was proved that the prophylactic use of penicillin and sulphonamides for long periods in people prone to rheumatic fever reduced considerably the incidence of relapses.

It is not known why some people develop acute rheumatism, scarlet fever, erysipelas, or nephritis in response to a streptococcal infection; presumably the

difference lies in the constitution of the individual, and this may account for the observation that scarlet fever generally attacks large, healthy, robust children, whereas those with rheumatic fever tend to be below average size and of poor physique. *Marianna Clark.*

The Q-T Interval in Rheumatic Disease in Children. TARAN, L. M., and SZILAGYI, N. (1951). *Brit. Heart J.*, **13**, 10. 6 figs, 7 refs.

A study was made of 140 rheumatic children, aged 6 to 16 years at the St. Francis Sanatorium, Long Island. Different observers assessed the degree of rheumatic activity and severity of the cardiac lesions, and the electrocardiographic findings. The duration of electrical systole, corrected for rate (QTc), was determined according to Bazett's formula several times for each child: 0·405 sec. was taken as normal; 0·44 sec. would be considered a moderate prolongation.

The larger group of 123 children was observed throughout a single admission period averaging 12 months for each child. In 33 the QTc was initially normal or only moderately prolonged; it became shorter during the stay in hospital: only a fifth of these had progressive heart disease. In 39 the QTc remained unchanged, and in a third of these, in whom the QTc was also prolonged, there were progressive heart lesions. In 51 the QTc became longer while in hospital: three-quarters of these had progressive heart disease. Where the QTc was initially prolonged as well as increasing, nineteen out of twenty had severe and progressive lesions: four of these died. The smaller group of seventeen children was observed over intermittent admission periods for an average total time of 4½ years per child. Where the QTc was little if at all prolonged and tended to become shorter, cardiac lesions were unimportant; but where QTc was initially considerably prolonged and tended to become still longer, lesions were or became severe.

The authors conclude that serial observations on the corrected systole time have a prognostic value. The prognosis is bad where systole remains prolonged over a long period of time, especially if it becomes progressively longer. *J. A. Cosh.*

Q-Tc Interval of the Electrocardiogram in Acute Rheumatic Carditis in Children. SOLOMON, N. H., and ZIMMERMAN, M. (1951). *Amer. J. Dis. Child.*, **81**, 52. 3 figs, 9 refs.

The authors determined the Q-Tc (Q-T interval corrected for cardiac rate) by Bazett's formula in 27 children with acute rheumatism, all but two having evidence of carditis, and in 25 controls. They consider 0·422 to be a satisfactory figure for the upper limit of normal, as in 23 of the 25 controls the value of Q-Tc was below this. Of the 25 patients with active carditis, in 21 the Q-Tc was greater than 0·422 on at least one occasion. A persistently increased Q-Tc is considered by the authors to indicate a continually active carditis and to be of corresponding prognostic value [although the supporting evidence given is not convincing]. *J. A. Cosh.*

Antihyaluronidase Content of Serum in Children Suffering from Hemolytic Streptococcal Infections, Rheumatic Fever and Other Diseases. [In English.] STOPPELMAN, M. R. H. (1950). *Acta paediatr., Stockh.*, **39**, 510. 1 fig., 7 refs.

The serum antihyaluronidase level was determined in 705 children by the mucin-clot prevention method of Quinn. There were considerable variations in healthy children, but on average the titre increased with age. The estimation was carried out on eleven children with active rheumatic fever, and in ten of these high titres were found, but in only three cases was the titre above the highest found in healthy children. The author concludes that the test may give useful confirmatory evidence in the diagnosis of rheumatic fever, but that it is certainly not diagnostic of the condition. It seems that the titre fell when the activity subsided, or when chemoprophylaxis was given. *R. S. Illingworth.*

Rheumatic Fever and Glomerulonephritis. A Clinical and Postmortem Study. HARTMAN, S. A., and BLAND, E. F. (1951). *Amer. J. Med.*, **10**, 47. 28 refs.

The association of rheumatic fever and glomerulonephritis has been investigated in 117 patients suffering from glomerulonephritis and in 188 post-mortem records of cases of rheumatic carditis. In the former series there was a total incidence of 6 per cent. of polyarthritis or rheumatic heart disease, and in 2·5 per cent. active rheumatism and nephritis co-existed. From records of the cases of rheumatic carditis it was found that five of the subjects had had acute glomerulonephritis at death, four chronic nephritis, and seven a proliferation of glomerular epithelium, but not sufficient to warrant the diagnosis of glomerulonephritis. *Henry Cohen.*

A Quantitative Study of Salicylate Therapy in Rheumatic Fever. (Quantitative Untersuchungen zur Salizyltherapie des rheumatischen Fiebers.) BLUMENCRON, W., and BORKENSTEIN, E. (1951). *Med. Welt*, **20**, 275. 2 figs, 10 refs.

Efficient salicylate therapy of rheumatic fever depends on correct selection of cases and an adequate level of the substance in the blood. The minimum level is 35 mg. per 100 ml. blood and must be reached quickly and maintained for some time. The rapid increase necessary can only be obtained by intravenous therapy.

The attainment of an effective blood level depends essentially on the degree of intolerance. Symptoms of indigestion prevent peroral exhibition of single doses as large as 2 g. or daily doses over 8 g., while such therapy for more than 3 days is generally impossible. Salicylate may be given successfully per rectum as an isotonic solution or in gruel in order to diminish the local irritation. By the rectal route single doses of up to 8 g. in isotonic solution or 5 g. in gruel, and daily doses of up to 16 g. (divided into two or three parts), can be given. By this means maintenance of an effective blood level is possible. By intravenous therapy only 2 g. in 10 per cent. solution can be given as a single dose. Repeated injection of 1 g. sodium salicylate, however, produces an effective blood level. The ethanolamine salt of salicylic acid gives a more persistent blood level with correspondingly fewer injections. The diminution of gastric upset when sodium bicarbonate is given is of no value, for the blood level remains low due to increased excretion.

Ideal blood levels may be obtained by an initial intravenous dose followed by maintenance by the rectal route. On subsidence of the acute stage, peroral therapy may be instituted. Observation of the serum salicylate level is essential in salicylate medication because the drug as a rule should be administered until the limits of tolerance are reached. *Norval Taylor.*

Rheumatic Fever Treated with Cortisone and ACTH. KEITH, J. D., and NEILL, C. A. (1951). *Canad. med. Ass. J.*, **64**, 193. 8 figs, 6 refs.

Acute Infectious Lymphocytosis in an Adult. MALAMOS, B., and STAMATELAKIS, A. (1951). *Lancet*, **1**, 148. 1 fig., 11 refs.

Hyperpyrexia with Cerebellar Damage in Acute Rheumatism. CRUICKSHANK, E. K. (1951). *Lancet*, **1**, 1052. 1 fig., 19 refs.

Chronic Articular Rheumatism (Rheumatoid Arthritis)

Salicylazosulfapyridine (Salazopyrin or Azopyrin) in Rheumatoid Arthritis and Experimental Polyarthritis. KUZELL, W. C., and GARDNER, G. M. (1950). *Calif. Med.*, **73**, 476. 14 refs.

Of thirty patients with rheumatoid arthritis treated with "salazopyrin" (salicylazosulphapyridine), one had to stop treatment because of the sudden onset of anaemia and another refused to continue after 2 days because of "nervousness"; fourteen gained no benefit, but in fourteen there was marked improvement. The ages of the last group (in five of whom the presence of ankylosing spondylitis was recorded) varied from 24 to 64 years, and the duration of illness from 1 to 15 years; daily doses of 1·5 to 4 g. salazopyrin were given for periods of 2 months to 1 year, all but one of the group being still in receipt of a daily maintenance dose. Improvement, shown by diminution in joint swelling, stiffness, and pain, always began during the first 7 to 14 days of treatment. All these patients became worse when treatment had twice to be interrupted because of a shortage of salazopyrin. Toxic effects included restlessness and sleeplessness, mild nausea, and, in one case, a skin rash; the authors state that in only one case (that referred to above) was there a toxic effect on haematopoiesis [although in one of the group improved by treatment a reduction in erythrocyte count and haemoglobin concentration is shown]. No significant effect was observed upon the erythrocyte sedimentation rate.

When salazopyrin was added in a concentration of 0·5 per cent. to the food of rats injected with the L-4 strain of pleuropneumonia-like organism (which produces a polyarticular arthritis) the incidence of arthritis was very slightly lower, and the survival rate higher, than in the control animals; when the concentration was raised to 1 per cent. and 3 per cent. the incidence of arthritis was higher than in the controls. Other rats and mice given 1 per cent. salazopyrin for periods up to 121 days showed no consistent variation in body weight or leucocyte count compared with untreated controls.

[The discrepancy between these results and those of Sinclair and Duthie (*Ann. rheum. Dis.*, 1949, **8**, 226) is attributed to the smaller and more prolonged dosage used in the present study; since improvement was always apparent within 2 weeks this explanation seems inadequate. In the absence of controls or of any quantitative measure of improvement the significance of these clinical results is debatable.] *H. McC. Giles.*

Calciferol in the Treatment of Tuberculous Peritonitis and Chronic Rheumatoid Arthritis. (Wplyw kalcyferolu na gruzlicźe zapalenie otrzewnej i przewlekle zapalenie stawów.) KRÓL, W. (1950). *Polskie Arch. Med. wewn.*, **20**, 133.

Calciferol was used in the treatment of eight cases of tuberculous peritonitis and the results were encouraging. It was found that the response to treatment was as good with small doses (3,000 units daily) as with massive doses (150,000 to 180,000 units daily). Improvement was seen in the patient's general condition, in a fall in erythrocyte sedimentation rate, and in return of body temperature to normal. The blood calcium level rose in all cases irrespective of the dosage; changes in phosphorus and non-protein nitrogen levels were less consistent; in some cases there was a fall in phosphorus level despite hypercalcaemia. The results obtained in two cases of chronic rheumatoid arthritis of doubtful tuberculous aetiology were also favourable, especially when calciferol was combined with injections of streptomycin. *J. T. Leyberg.*

Severe Polyneuritis following Gold Therapy for Rheumatoid Arthritis. DOYLE, J. B., and CANNON, E. F. (1950). *Ann. intern. Med.*, **33**, 1468. 10 refs.

A patient developed polyneuritis after receiving 100 mg. "myochrysine" each week for 9 weeks. The symptoms consisted of tingling in the extremities with muscular weakness and incoordination. The cerebrospinal fluid was normal. The condition became worse for about a month after administration of myochrysine ceased and thereafter gradually improved with complete recovery by 4 months later. *V. J. Woolley.*

Intravenous Iron in Treatment of Hypochromic Anaemia associated with Rheumatoid Arthritis. SINCLAIR, R. J. G., and DUTHIE, J. J. R. (1950). *Brit. med. J.*, **2**, 1257. 7 refs.

Anaemia, either hypochromic or normochromic in type, is found in association with all forms of infection. It is common in rheumatoid arthritis. Sinclair and Duthie in 1949 described the response of 23 cases to intravenous iron; they have now treated a further 28 cases, making 51 in all. These patients all proved resistant to oral iron. A satisfactory rise in haemoglobin value was found in 38 cases but thirteen remained refractory and only two of these responded to a second course of iron. In a further thirteen cases the haemoglobin level was maintained for as long as 23 months without further treatment and three cases which responded initially required a further dose. Ascorbic acid given intravenously was without effect on the refractory cases. The authors consider that iron absorption, as measured by the effect of oral iron on the plasma iron level, was normal even in refractory cases. They conclude that the anaemia is due to an increased need of the tissues for iron, a need which cannot be met by absorption of iron given by mouth. It is clear that experimental observations with radioactive iron might throw interesting light on the mechanism of this type of anaemia. The cases which responded to oral iron showed a rapid fall in the erythrocyte sedimentation rate. It is suggested that the anaemia alone cannot account for the high rate and that there must be some associated change in serum protein levels. Apart from interesting theoretical considerations raised by this paper, it is encouraging to know that in some cases of

rheumatoid arthritis the anaemia can be relieved, a finding which is not corroborated by the work of Wintrobe and his colleagues (*J. clin. Invest.*, 1950, **29**. 1505). *Janet Vaughan.*

Arteritis of Striated Muscle in Rheumatoid Arthritis. SOKOLOFF, L., WILENS, S. L., and BUNIM, J. J. (1951). *Amer. J. Path.*, **27**, 157. 9 figs, 10 refs.

Biopsy of striated muscles revealed an arteritis in five out of 57 cases of rheumatoid arthritis. The lesion was not directly connected with the affected joints, as the portions of muscle sectioned were taken at areas remote from them. A specific lesion is thought to have been found in view of the constancy of its anatomical location and because similar lesions were not encountered in other conditions. The vessels involved were large arterioles or small arteries. The histological features were not distinctive, and consisted of a granulomatous inflammation which might be localized in the adventitial or extend through all three arterial coats. Neither endothelial destruction nor collagenous necrosis was seen and thrombosis did not occur. In discussing the lesion a useful comparative table is given showing the main differences in several types of arteritis.

[It is unlikely that this lesion will be of diagnostic value in view of its infrequency and the fact that only a few of a large number of serial sections showed the histological changes. This probably accounts for the negative findings of earlier workers.] *G. J. Cunningham.*

Plasmacytosis in the Bone Marrow in Rheumatoid Arthritis. HAYHOE, F. G. H., and SMITH, D. R. (1951). *J. clin. Path.*, **4**, 47. 5 figs, 18 refs.

The possibility of a connexion between plasma cells, antibody formation, and hyperglobulinaemia was studied in the Department of Medicine, Cambridge University. In ten consecutive cases of rheumatoid arthritis of variable duration and severity, bone marrow was examined, plasma protein levels were estimated by a micro-Kjeldahl technique, and erythrocyte sedimentation rate was measured. The plasma-cell elements of the marrow were classified as plasmablasts, proplasmacytes, plasmacytes, plasmacytes showing early homogeneous degeneration, and degenerative plasmacytes. The proportion of all plasma cells in the preparations was 1·8 to 6·3 per 100 marrow cells. A finding of more than 2 per cent. is certainly abnormal, but even figures higher than 3 per cent., the presence of nuclear and cytoplasmic abnormalities in plasma cells, and the finding of multinucleated cells are not absolutely diagnostic of multiple myelomatosis without supporting evidence. A definite increase in the plasma globulin level was noted in every case. It is suggested that the hyperglobulinaemia of rheumatoid arthritis is an antibody response, accompanied by plasmacytosis, to an unknown antigen.

[These findings agree substantially with those of Leitner, Britton, and Neumark (*Bone Marrow Biopsy*, 1949). It is probable that plasma cells are concerned with the production of globulins.] *E. Neumark.*

Felty's Syndrome. A Report of Four Cases Treated by Splenectomy. HUTT, M. S. R., RICHARDSON, J. S., and STAFFURTH, J. S. (1951). *Quart. J. Med.*, **20**, 57. Bibl.

Felty's syndrome is defined as a triad of rheumatoid arthritis, splenomegaly, and neutropenia. This association of signs had been noted by many workers long before Felty (1924) recognized it as a clinical entity and gave a description of five cases in middle-aged men and women. The paper deals with four cases, one male and three female. Splenectomy was performed in all of them with good results. The most striking feature was the improvement in general health, which was found to be maintained a year later. Eye complications such as corneal ulcer and hypopyon tended to clear up; ulcers in the mouth and on the legs healed well. The leucocyte count was restored to normal, which is held responsible for most of the improvement. The arthritis also improved. Some of the features of the syndrome are ascribed to hypersplenism, whose *modus operandi* is discussed. The authors urge the use of splenectomy in Felty's syndrome, unless there are definite contra-indications. *D. Preiskel.*

The Manubrio-sternal Joint in Ankylosing Spondylitis. SAVILL, D. L. (1951). *J. Bone Jt Surg.*, **33B**, 56. 14 figs, 13 refs.

The radiological appearances of the manubrio-sternal joint in a series of 61 cases of ankylosing spondylitis are described, comparison being made with a similar group of healthy persons and a smaller group of patients with polyarticular rheumatoid arthritis. Narrowing and eventual fusion of the joint were found in a high proportion of the patients with spondylitis, all those over 35 years of age showing this feature. The changes in the manubrio-sternal joint are regarded as similar to those found in the sacro-iliac joint.

The superficial location of the manubrio-sternal joint made it possible to undertake biopsy examination in five cases, including one in which the joint was fused. The cartilage was found to be replaced by fibrous tissue which involved the adjacent bone ends, but which did not show any inflammatory reaction. *H. A. Sissons.*

(Osteo-Arthritis)

Denervation as Treatment for Arthrosis Deformans Coxae. [In English.] HIERTONN, T. (1950). *Acta orthopaed. scand.*, **20**, 64. 5 figs, 39 refs.

All the recent literature on the anatomy of the nerve supply to the hip-joint is surveyed.

Obturator neurotomy or neurectomy alone is insufficient to bring about adequate relief of pain in arthritis, be it "primary" or secondary to such conditions as subluxation, slipped femoral epiphysis, or unhealed arthrodesis. There are cases, however, where the more radical operations of arthrodesis and arthroplasty with total capsulectomy are not indicated, especially in patients too old or frail to withstand major operations or those with a good range of movement.

The author treated 54 patients by denervation at the Karolinska Institute, Stockholm, one patient undergoing bilateral denervation. All patients underwent obturator neurectomy, combined with section of the nerve to the quadratus femoris and gemellus inferior. This latter nerve supplies part of the posterior aspect of the joint. At 43 operations the obturator nerve was carefully dissected out by an anterior intrapelvic, extraperitoneal approach, combined with posterior operation through a transverse incision across the buttock, through the gluteus maximus and with medial retraction of the

sciatic nerve. These patients fared somewhat better than those who had undergone simple division of the two nerves without careful search for all branches given off high up. All the same, only in 50 per cent. of cases was improvement noted and in no case was complete sensory denervation of the joint achieved.

Elliot E. Philipp.

Arthroplasty of the Hip ad modum Smith-Petersen. A Survey. [In English.] ALVIK, I. (1950). *Acta orthopaed. scand.*, **20**, 78.

A series of 24 cases of arthroplasty of the hip carried out by the Smith-Petersen technique at the Sophies Minde Clinic for Cripples, Oslo, is reviewed.

The average age of the patients was 42·25 years, the youngest being 17 and the oldest 63. Six patients with bilateral arthritis, who had undergone operation only on one hip, showed marked clinical deterioration in the side which had not been operated upon. Results were excellent in four cases, satisfactory in 31, and unsatisfactory in six. In one case, the condition was worse. The presence of a few degrees of hyperextension at the hip is more important for walking than is a marked degree of flexion. The best indication for the operation is unilateral arthritis in a patient with a sedentary occupation and severe symptoms. Gables show the degrees of movement obtained and the functional results. *Elliot E. Philipp.*

(Spondylitis)

Marie-Strümpell Arthritis. Follow-up Study of Roentgenographic, Physical, and Orthopaedic Therapy. BAKER, L. D., COONRAD, R. W., REEVES, R. J., and HOYT, W. A. (1950). *J. Bone Jt Surg.*, **32A**, 848, 866. 3 figs, 15 refs.

In a series of 100 patients with Marie-Strümpell arthritis valuable results were obtained with radiotherapy. This treatment is used at any stage in the disease and an increase in mobility can be expected in a fair percentage of the mild and moderately advanced cases. In the mild and moderate cases they discovered fifteen out of 47 patients in whom the *x*-ray appearances improved under this treatment. *John Charnley.*

Iritis associating with Spondylitis Ankylopoietica. CHAN, E., and SUN, S. F. (1951). *Chinese med. J.*, **69**, 147. 5 refs.

A Chinese business man aged 26 who suffered from a seriously deformed spine and hip joints for a number of years, was diagnosed to have ankylosing spondylitis. He suffered concurrently from repeated attacks of iritis. The articular as well as ocular findings are recorded in detail. The possibility of iritis as a pointing sign in this type of joint disease is suggested. (*Authors' summary.*)

(Miscellaneous)

Studies of the L.E. Phenomenon. BARNES, S. S., MOFFAT, T. W., LANE, C. W., and WEISS, R. S. (1950). *Arch. Derm. Syph., Chicago*, **62**, 771. 4 figs, 9 refs.

The authors have confirmed the work of previous investigators on the lupus erythematosus (L.E.) phenomenon (presence of L.E. cells with the formation of clumps and rosettes in the blood). The phenomenon is not an artefact and is unrelated to the addition of anticoagulant.

Serum from patients with chronic discoid or disseminated discoid L.E. does not produce the phenomenon, nor does serum from other diseases in the so-called collagen group or from samples of blood with a high-titre syphilitic reaction. The L.E. phenomenon is a constant observation in acute lupus erythematosus in the active stage; it may be useful in diagnosis of fever of unknown origin. Previously undescribed inclusion bodies of oval shape are presented and are thought to be stages in the development of the L.E. body; two tests are described whereby L.E. cells can be induced to develop in normal leucocytes.

Sternal marrow in cases of subacute lupus erythematosus disseminatus usually gives negative results, but in some cases the blood serum may give definite positive results. *G. A. Hodgson.*

The Heparin Tolerance Test in Lupus Erythematosus. BORRIE, P. (1951). *Brit. J. Derm.*, **63**, 21. 33 refs.

The ground substance of collagen is closely related to heparin. In collagenous diseases it is presumed that there is circulating in the blood a substance antagonistic to this ground substance and therefore to heparin. Investigation of ten patients with acute lupus erythematosus showed that the blood contained a factor which inhibited the action of heparin to the same degree as that found in rheumatic fever. The bearing of this upon cortisone therapy is discussed. *John T. Ingram.*

Tonsillectomy in Chronic and Postacute Rheumatoid Arthritis. [In English.] RICHTNER, N. G. (1950). *Acta otolaryng., Stockh.*, **38**, 419.

The author has studied the effect of tonsillectomy in cases of polyarthritis. Of 860 patients (283 males and 577 females), 432 (149 males and 283 females) underwent tonsillectomy. A careful history was taken of ear and throat conditions, especially of throat infections; a positive history and, in some cases, a raised erythrocyte sedimentation rate influenced the decision to operate. In 164 cases the tonsils were examined histologically and on the basis of the pathological findings the cases were divided into two groups: (1) 110 cases with definite signs of inflammation of the tonsils; (2) 54 cases with signs of hyperplasia only, and little or no inflammatory change.

On studying the incidence of these findings as regards positive and negative pharyngeal histories the authors concluded that even with a positive tonsillar history it was not possible to form any definite opinion what the pathological findings would be. No statistically significant difference in the mean erythrocyte sedimentation rate was found between the tonsillectomy group and the control series, even when the cases were classified as regards positive and negative pharyngeal history and positive and negative tonsillar findings.

The author points out that American investigators have recently advanced the view that chronic polyarthritis is probably associated more with metabolic disturbances rather than with infectious conditions. No significant difference was noted in the tonsillectomy series as regards the joints involved on the patient's admission to and discharge from hospital.

E. D. Dalziel Dickson.

Alteration in Blood Proteins in Rheumatic Patients. BROWNING, J. S., RICE, R., and ULRICH, C. (1951). *Amer. J. med. Sci.*, **221**, 183. 14 refs.

Serum gamma globulin and antistreptolysin titre were estimated in 78 patients with rheumatic conditions, and in 35 normal controls. The mean level of gamma globulin in normal subjects was 0·882 G. A gamma globulin value of over 1·0 G. was found in most patients with rheumatoid arthritis and rheumatic fever. The antistreptolysin titre was invariably raised in rheumatic fever, but only about a quarter of the patients with rheumatoid arthritis showed a similar rise.

The authors conclude that there is no correlation between these two values, and that the gamma globulin estimation is only of limited value: its estimation is a complex procedure. *B. E. Mace.*

Some Problems concerning Kerato-conjunctivitis Sicca and the Sicca Syndrome. SJÖGREN, H. (1951). *Acta ophthal., Kbh.*, **29**, 33. 4 tab., 9 refs.

Disseminated Lupus Erythematosus in the Male. Report of Five Cases. PASTOR, B. H., SLOANE, N. G., and GOLDBURGH, H. L. (1951). *New Engl. J. Med.*, **244**, 81. 10 refs.

Reiter's Syndrome: Apparent Recovery. Treatment with Aureomycin. GRIEP, A. H., and LEICH, C. F. (1951). *Univ. Mich. med. Bull.*, **17**, 18. 13 refs.

Articular Rheumatism as a Disturbance of the Vegetative Nervous System. (Der Gelenkrheumatismus als vegetative Regulationsstörung.) BRAEUCKER, W. (1951). *Med. Klinik.*, **46**, 41.

Significance to the Physiatrist of Recent Developments in Rheumatic Diseases. POLLEY, H. F., and ELKINS, E. C. (1951). *Arch. phys. Med.*, **32**, 146. 1 fig., 7 refs.

Sciatica

Orthopaedic Signs in the Diagnosis of Disc Protrusion, with Special Reference to the Straight-leg-raising Test. CHARNLEY, J. (1951). *Lancet*, **1**, 186. 6 figs, 8 refs.

In this paper an attempt is made to correlate physical signs seen in patients with sciatica with the findings at operation and the subsequent progress. The close correlation between limitation of straight-leg-raising (S.L.R.) and limitation of forward flexion of the trunk on standing is demonstrated, and patients seen are classified in three ways: (1) Those in whom there is marked limitation of S.L.R. and of forward flexion; in this group disk prolapse is nearly always found at operation and subsequent progress is good. (2) Those with little or no limitation of S.L.R. and forward flexion; these commonly do not show a disk prolapse or obtain relief from laminectomy. In these patients the sciatica is assumed to be due to stretching of an abnormally sensitive nerve root. (3) Those with marked discrepancy between limitation of forward flexion and S.L.R. These rarely show a disk prolapse and do badly after operation: it is suggested that some of these patients are psychoneurotics.

The reversal of the normal lumbar lordosis is ascribed to the wedging effect of the posteriorly projecting disk rather than a reflex mechanism to relieve tension upon the sciatic nerve. Scoliosis, which is seen in many of these patients, is often transitory and seems by itself to be of little significance.

A method of establishing an axis of flexion for the lumbar spine as a whole is described, and from radiographic measurements of movements in the cadaver it is stated that this axis lies in the posterior quarter of the intervertebral disk. Flexion and extension of the spine thus cause little change in the position of the anterior dura and nerve roots, and the tension placed on the sciatic nerve either in straight-leg-raising or in forward spinal flexion is due to flexion at the hip-joint. This stretching is maximal in the arc 40 to 60°. *Peter Ring.*

Non-Articular Rheumatism

General Symptoms in Scapulo-humeral Periarthritis. (Almensymptomer ved periarthrosis humeroscapularis.) MEULENGRACHT, E. (1950). *Ugeskr. Laeg.*, **112**, 1711. 6 figs, 12 refs.

In 1945 the author described several cases of scapulohumeral periarthritis, the condition being associated with prolonged fever, loss of weight, and a high erythrocyte sedimentation rate. He has now analysed all cases of this condition admitted to one of the medical units of the Bispebjerg Hospital, Copenhagen, between 1945 and 1950 (a total of 82 cases), in order to establish the incidence of generalized symptoms and signs.

In sixteen cases there was low fever, a temperature of about 38° C. (100·4° F.) lasting for at least several weeks and in some cases for 6 months and even longer. The erythrocyte sedimentation rate was raised in 53 cases, in 24 of them above 50 mm. in one hour. In no less than sixteen cases the condition complicated thyrotoxicosis. Fleeting pains in various parts of the body often preceded the local condition, and soft-tissue involvement in the hands, including contractures, is also described. *W. G. Harding.*

Tendovaginitis Stenosans (Maladie de Quervain). [In English.] MULLER, H. (1950). *Arch. chir. neerl.*, **2**, 188. 4 figs, 11 refs.

The author surveys the literature and reports eight cases of typical Quervain's disease and one case of stenosing tendovaginitis involving the second and third compartments of the carpal ligament. The author supports the view that the primary changes are in the dorsal carpal ligament, and he stresses that a portion of the tendon sheath should be removed. *J. Agerholm.*

De Quervain's Disease. KOEN-COHEN, B. (1951). *J. Bone Jt Surg.*, **33B**, 96. 3 figs, 3 refs.

General Pathology

An Anatomical Study of the Human Spinal Column: with Emphasis on Degenerative Changes in the Cervical Region. MORTON, D. E. (1950). *Yale J. Biol. Med.*, **23**, 126. 7 figs, 24 refs.

The degenerative changes associated with the ageing process in the spinal column were studied in forty unselected cadavers, 35 male and five female. The spinal columns were inspected after division by a mid-sagittal

cut through the centra, but only the cervical regions were dissected and measured. The age at death ranged from 36 to 82 years and averaged 64·6 years.

Brown degeneration of one or more intervertebral disks was observed in 70 per cent. of the cadavers and fissuring in 30 per cent., but neither change was consistently associated with other spinal changes. Posterior thinning of the disks was observed more frequently in the cervical and lumbar regions while anterior thinning was more prominent in the thoracic region. Schmorl's nodules (54) were noted in 27 cadavers, with a higher incidence in the older specimens. The lumbar region had the smallest ratio of nodules to the number of disks. There was no constant correlation between them and other degenerative changes, and they did not appear to be prime factors in producing other forms of degeneration. A partial anterior herniation of the nucleus pulposus through the annulus fibrosus was noted once, but fourteen posterior herniations were observed in eight specimens. Eight of these (six midline) indented the spinal cord and one aided in compressing a cervical nerve. Degenerative changes in the disks and vertebral bodies were not consistently associated with herniation. Posterior protrusion of one annulus fibrosus or more 2 mm. or more into the vertebral canal was observed in 77·5 per cent. of specimens, with posterior thinning of the disks a constant accompanying feature.

Changes in the vertebral bodies consisted of: (1) shortening but widening of the centra of C5 and C6; (2) eburnation of the bodies at 21 disk levels in nine cadavers, which was always accompanied by thinning of the corresponding disk; (3) antero-lateral or posterior hypertrophic lipping at the edges of the bodies in 90 per cent. and 80 per cent. of the specimens respectively. Lipping did not constantly accompany disk changes, approximately half the disks being normal. Posterior lipping caused indentation of the cord in 22·5 per cent. and was the predominant cause of a decrease in the antero-posterior diameter of the intervertebral foramina. Postero-lateral exostoses compressed spinal nerves in 20 per cent. of specimens, both these conditions being mainly in the cervical region. Hypertrophic or mixed arthritis of the articular processes was observed in six specimens; this was always accompanied by thinning of the disk at the corresponding level. *A. Ackroyd.*

Hyaluronidase Inhibitor of Human Blood Serum in Health and Disease. GLICK, D. (1950). *J. Mt Sinai Hosp.*, **17**, 207. 3 figs, 21 refs.

The author describes the results of an investigation into the effects of various diseases on the level of non-specific inhibitor of hyaluronidase in serum as estimated, by the viscosimetric method of Glais and Glick (*J. invest. Derm.*, 1948, **11**, 259). The blood level of hyaluronidase inhibitor was measured in 27 cases of poliomyelitis and the results compared with those in thirty normal subjects. A significant elevation above the normal was found, and follow-up studies on nine patients showed that the magnitude of the inhibitor value was proportional to the severity of the disease. Similar results were obtained on three monkeys and 128 mice which had been experimentally infected. In order to test the specificity of this phenomenon measurements were made on 127 patients exhibiting a wide variety of bacterial and virus diseases and the values compared with those obtained from 211 normal sera. It was concluded that the elevation of inhibitor values in blood serum in infectious diseases was non-specific, but that an essential requirement for elevation was acute systemic involvement. The effect of vaccinia vaccination on the serum inhibitor level of 35 college students was also studied; in sixteen individuals with immune reactions negligible changes in the inhibitor level were observed, but in the other nineteen subjects the magnitude of the elevation paralleled the intensity of the reaction.

The author found a significant elevation of serum inhibitor level in twenty cases of acute rheumatic fever and again in ten cases of acute streptococcal pharyngitis. Subnormal inhibitor values were observed in ten cases of convalescent rheumatic fever and in fifty cases of inactive rheumatic fever; it is suggested that the lowered inhibitor level might be a factor in enhancing the susceptibility of these patients to rheumatic disease. In five children suffering from hypoglycaemia and treated with 9 mg. adrenocorticotrophin (ACTH) every 6 hours over a 4-day period, it was found that a significant rise in the serum inhibitor level was produced by the ACTH treatment and that it reverted to slightly below the pre-injection level 7 days after the termination of hormone therapy. The abnormally high serum inhibitor levels found in cases of rheumatic fever were reduced to normal during ACTH treatment, but rose again when therapy was discontinued. Significant elevations of serum inhibitor level were observed in animals subjected to stress, and it was found in rats that adrenalectomy abolished the rise in the serum inhibitor level normally caused by chilling. It was concluded that the adrenal cortex may play an essential role in controlling the fluctuation of serum hyaluronidase inhibitor level.

An investigation of the occurrence of hyaluronidase in human malignant tissue was undertaken, and clean, non-necrotic specimens of tissue obtained under sterile conditions from four benign and six malignant tumours were extracted under aseptic conditions. Specimens from 25 malignant tumours and 25 specimens of normal tissue which were directly contaminated by bacteria were also extracted, and it was found that neither benign nor malignant tumours possessed any hyaluronidase activity other than that contributed by micro-organisms containing the enzyme. Significantly high serum concentrations of hyaluronidase inhibitor were found in 32 cases of malignant tumour which had undergone metastases, as compared with 75 normal subjects and 25 cases of benign and thirty of malignant but non-metastatic tumour. It was concluded that elevation of the serum inhibitor level occurs in cancer only when the disease has progressed to the stage of a systemic reaction. *M. J. H. Smith.*

A Method for Detecting Cortisone in Body Fluid. COPE, C. L. (1951). *Brit. med. J.*, **1**. 271. 1 fig., 6 refs.

A simple method is described for the extraction of cortisone-like material from urine. The material is injected into adrenalectomized mice and its effect on the number of circulating eosinophil cells is measured. Preliminary results showed that cortisone-like activity was absent from the urine of patients with Addison's disease and hypopituitarism but increased during ACTH administration, in late pregnancy, and in a patient with an adrenal cortical carcinoma. *A. C. Crooke.*

Failure of Adrenalectomy Immediately following Stress to Prevent Eosinopenia in Rats. LOVE, W. D. (1950). *Proc. Soc. exp. Biol., N.Y.*, **75**, 639. 1 fig., 7 refs.

Male and female albino rats of the Fairfield strain, weighing 125 to 250 g., were used. The animals received 0·2 mg. adrenaline per kg. subcutaneously and were then restrained in a tail cage for 4 hours. Eosinophil counts were made by a modification of the Randolph technique (*J. Allergy*, 1944, **15**, 89) on tail blood at 10 minutes, 2 hours, and 4 hours after the injection. A total of 0·57 c.mm. blood was counted in aqueous 50 per cent. propylene glycol with 0·1 per cent. eosin.

Single-stage adrenalectomy was performed under ether, the time required to complete the operation being measured from the time the animal was first picked up to the clamping of the second adrenal pedicle.

It was found that an eosinopenia followed stress even though adrenalectomy was complete within 10 minutes, and that the continued normal 4-hour fall in circulating eosinophils took place in the absence of continued secretion of the adrenal cortex. *Norval Taylor.*

Liberation of Adrenaline from the Suprarenal Gland of the Rabbit. WEST, G. B. (1950). *Brit. J. Pharmacol.*, **5**, 542. 1 fig., 13 refs.

By means of parallel biological assays the amounts of adrenaline and noradrenaline in the adrenal glands of the rabbit and in adrenal venous blood before and during splanchnic stimulation were estimated. Adrenal glands were taken after death, the capsule removed, and the gland ground with sand and 10 ml. 0·1N hydrochloric acid per g. The extract was filtered and assayed. Adrenal blood was collected in eviscerated rabbits anaesthetized with urethrane from a cannula in the vena cava between ligatures which closed all veins other than the left adrenal vein. The blood was rapidly cooled and centrifuged and the plasma assayed.

The tests employed were on: (1) fresh rabbit ileum, which was twice as sensitive to adrenaline as to noradrenaline (A/N ratio 0·5); (2) rabbit ileum stored 4 days at 4° C. (A/N ratio 3·0); (3) blood pressure of rabbit anaesthetized with urethane, treated with cocaine 8 mg. per kg., and with the vagi cut (A/N ratio 0·5); (4) isolated rectum of week-old chick (A/N ratio 0·05); (5) isolated uterus of rat in dioestrus (A/N ratio 0·02).

The sympathin obtained was principally adrenaline. This was the case with sympathin extracted from the gland and also with that from the adrenal venous blood. In ten rabbits when the left gland was stimulated before it was removed the mean concentration of adrenaline was 568 mg. per g. compared with 418 mg. per g. in the right (range 400 to 890 mg. and 225 to 756 mg. respectively). In nine rabbits where neither gland was stimulated the means were: left 472, right 498 mg. per g. Noradrenaline was detected only twice, each time in unstimulated glands and amounting to about 10 per cent. of the total sympathin. In twelve rabbits the mean adrenaline concentration in plasma from the adrenal vein was 0·084 mg. per ml. Noradrenaline was detected in plasma from three of the rabbits in concentrations of 0·02, 0·01, and 0·03 mg. per ml. During splanchnic stimulation the amount of adrenaline rose and noradrenaline was detected more often. The amount of noradrenaline was greatest in the samples collected between the 9th and 12th minutes of stimulation, when the percentage of adrenaline fell to 68. Adrenaline only was detected after the 15th minute of stimulation. *R. P. Stephenson.*

Studies on Salt Hypertension. Effects of Adrenalectomy and Nephrectomy. BRANDT, W. L., DUBIN, W. M., and SAPIRSTEIN, L. A. (1951). *Amer. J. Physiol.*, 164, 73. 3 figs, 11 refs.

Twenty rats were given a 2 per cent. sodium chloride solution instead of drinking water, and all developed hypertension and cardiac hypertrophy at the end of 6 weeks. The animals were further subdivided into two groups of twelve and eight, the first being subjected to bilateral adrenalectomy, and the second to an equivalent operation in which the adrenals were manipulated but not removed. After the operation, the rats continued on sodium chloride and, at the end of 4 weeks, it was noted that the blood pressure both in sham-adrenalectomized controls and in adrenalectomized animals remained at a comparable high level. It is concluded that salt hypertension, once established, persists in spite of total adrenalectomy. Furthermore, in the adrenalectomized rats cardiac hypertrophy disappeared despite the persistence of hypertension. In other experiments it was shown that salt hypertension is a reversible process and can be made to disappear by replacing sodium chloride with tap water. In a group of seven salt-induced hypertensive rats, bilateral nephrectomy was performed. The hypertension persisted as long (about 3 days) as the animals survived.

It appears that salt-hypertension in rats is not mediated through the adrenal gland or kidney. *A. I. Suchett-Kaye.*

Variation and Error in Eosinophil Counts of Blood and Bone Marrow. BEST, W. R., and SAMTER, M. (1951). *Blood*, **6**, 61. 10 figs, 35 refs.

The sources of error inherent in the chamber eosinophil count are described: 99 per cent. of observations in 143 successive clinical determinations were found to lie within the expected limits as calculated from the formula. The theoretical limits of chance variation in differential eosinophil counts in marrow smears were calculated with the chi-square formula, but the observed error exceeded this estimate, a finding attributed to clumping of eosinophils. Peripheral eosinopenia induced by adrenocorticotrophin (ACTH) was not accompanied by any significant change in marrow eosinophils.

The physiological variations in eosinophil counts are reviewed. Serial counts show a significant diurnal variation with considerable minute-to-minute fluctuations superimposed upon it; 38 per cent. of normal subjects had a maximum morning fall of eosinophils of at least 50 per cent. A single eosinopenic response to ACTH or adrenaline is not an unequivocal test for the integrity of the hypothalamus-pituitary-adrenal chain, and repeated and controlled observations are necessary. Ephedrine was as effective an eosinopenic agent as adrenaline. *P. C. Reynell.*

Disturbance of Liver Function in Rheumatism. (О нарушении Функционального состояния печени при ревматизме) LORMAN, M. L. (1951). *Klin. Med., Mosk.*, No. 1, 86.

Severe disturbance of liver function is rarely found in patients suffering from rheumatism, but milder changes are not uncommon. The author describes 76 cases of

rheumatoid arthritis which were investigated from this point of view. In fifteen cases, in seven of which there was no heart lesion, the liver showed marked enlargement, but in all it returned to normal on recovery. In 66 cases there was disturbance of water metabolism, the 24-hourly output being only 65 to 75 per cent. of the intake, and recovery was followed by diuresis. In 59 cases McClure's blister test was positive. The surface tension of the urine was lowered in 66 cases, due in all probability to the presence of bile acids. Ehrlich's aldehyde reaction for urobilinogen was positive in 54 cases, and the Takara-Ara reaction in thirteen. These returned to normal after recovery.

L. Firman-Edwards.

Experimental Investigations regarding the Amount of Mucopolysaccharides in the Tendons after Prolonged Muscular Strain. [In English.] WRETE, M. (1950). *Acta orthopaed. scand.*, **20**, 166. 1 fig., 4 refs.

Prolonged exercise of guinea-pigs did not produce any conspicuous morphological changes in the Achilles tendon, though a chemical analysis showed an increase of mucopolysaccharides. *J. Agerholm.*

The Nutritive Supply and Nutritional Value of Synovial Fluid. [In English.] INGELMARK, B. E. (1950). *Acta orthopaed. scand.*, **20**, 144. 5 figs, 16 refs.

Previous observations had shown that the medullary cavity is in some places in direct contact with the basal part of the articular cartilage without any intervening bone lamella. When rice starch was injected into the medullary cavity of the epiphyses of newly-killed rabbits, starch grains were found in the basal and central parts of the cartilage. If the joints were subjected to repeated compression after the injection, most of the grains were found in the upper and medial portion of the articular cartilage, and some were found in the synovial fluid. The findings were similar when the starch was injected intravenously in live rabbits. Similar contacts were found in man as well.

Special radiological investigations proved that the thickness of the articular cartilage rapidly increases when the joints are subjected to repeated compression and that it decreases when this stress ceases. Normal and pathological knee-joints were examined in this way.

J. Agerholm.

The Chemistry of Synovial Fluid with Special Regard to Hyaluronic Acid. [In English.] SUNDBLAD, L. (1950). *Acta orthopaed. scand.*, **20**, 105. 1 fig., 12 refs.

Estimations of the hyaluronic acid content, the viscosity, and the protein content of synovial fluids were carried out in man and animals. The high viscosity of the synovial fluid is due to its content of hyaluronic acid and is approximately in inverse proportion to the volume of fluid. In pathological joints the protein content was found to be low in degenerative conditions, moderately increased in traumatic ones, and greatly increased in rheumatic and infective arthritis, while the hyaluronic acid content was found to be low in the traumatic effusion and relatively high both in degenerative and in infective or rheumatic arthritis.

J. Agerholm.

The Protein Pattern of Joint Exudates. [In English.] OLHAGEN, B. (1950). *Acta orthopaed. scand.*, **20**, 114. 1 fig., 8 refs.

The protein content of normal synovial fluid is 1 to 2 g. per 100 ml. In 45 pathological cases it was found to be about 6 g. per 100 ml. in infective and about 4 g. per 100 ml. in non-infective exudates. Qualitative analysis by electrophoresis showed that in acute exudates the relative concentrations of the different protein components corresponded to those of plasma, but in chronic exudates that of fibrinogen was reduced and eventually disappeared and that of gamma globulin was increased.

J. Agerholm.

ACTH, Cortisone, and Other Steroids

Effect of Cortisone and Pituitary Adrenocorticotropic Hormone (ACTH) on Rheumatic Diseases. HENCH, P. S., SLOCUMB, C. H., POLLEY, H. F., and KENDALL, E. C. (1950). *J. Amer. med. Ass.*, **144**, 1327. 1 fig., 37 refs.

The anti-rheumatic properties of cortisone and pituitary adrenocorticotrophic hormone (ACTH) have been confirmed by several groups of investigators.

During the time of their administration, these hormones have exerted a decidedly suppressive effect on the clinical and biochemical manifestations of rheumatoid arthritis. When the use of the hormones is discontinued symptoms recur rather promptly in most cases, but in several of our cases pronounced improvement has persisted for several (7 to 14) months. The optimal dosage and methods of administration of these hormones for the investigative management of a chronic disease such as rheumatoid arthritis remain to be determined. Several schemes are under investigation. Rather prolonged relief with minimal side effects has been provided in some cases by the continued use of small maintenance doses after the earlier use of larger suppressive doses.

Cortisone or pituitary adrenocorticotrophic hormone generally abolishes quickly the manifestations of acute rheumatic fever. There is reason to believe that the lesions of acute rheumatic carditis also are suppressed, in consequence of which the prevention of certain chronic cardiac lesions may be anticipated with some confidence, especially if adequate hormonal usage during the acute rheumatic state is followed by prolonged chemoprophylaxis (for example, with penicillin given orally). The articular complications of disseminated lupus erythematosus and psoriasis are responsive to these hormones. Limited results were obtained in 2 cases of tuberculous arthritis.

These hormones are powerful agents which may affect many functions and tissues of the body besides those of joints and muscles. Their prolonged use, at least in certain doses, may produce certain undesirable effects. These side effects have, to date, been transient and reversible. Certain measures have been developed to minimize or control some of them, but these effects still constitute an important problem for further investigation. If control of the side effects is not adequate in any given case, smaller doses of the hormones should be used and patient and physician alike should be content with a reduced amount of symptomatic relief.

With the exception of 17-hydroxycorticosterone (compound F of Kendall), none of the currently available

steroids chemically related to cortisone appears to have significant anti-rheumatic properties. The oral administration of one specially prepared extract of adrenal cortex containing compounds E (cortisone) and F produced appreciable relief in one case of rheumatoid arthritis and has lent support to the belief that cortisone, and perhaps also compound F, will be chemically effective when given orally.

The mode of action of cortisone and pituitary adrenocorticotrophic hormone in rheumatic diseases is not yet known, but the hormones appear to provide to the tissues affected in these diseases a shield-like buffer against a variety of irritants.

The results of recent and current investigative studies appear to provide justification for the impending restricted application of these hormones to the field of therapy, at least in certain acute rheumatic and articular conditions.—[*Authors' summary.*]

Cortone Therapy in Acute Gout. BLOOM, N., and TOONE, E. (1951). *Va med. Mon.*, **78**, 84. 2 refs.

This is a detailed report of a single case of gout treated by cortisone. A male aged 46 began to suffer attacks of acute pain and swelling in the toe in 1941, after the surgical removal of aberrant thyroid tissue from a lobe of the gland. This was " recognized as gout ". Several periodic attacks followed, related to " excessive mental effort ". In May, 1947, there was gouty arthritis in the knees with 7 weeks' disability. A repetition in 1949 in the left knee caused disability for 2 weeks. In May, 1950, an attack began as cramp in the calf muscle spreading to typical gouty arthritis in the left knee. Cortisone therapy was now started, 1,155 mg. being given in 17 days. " No further sedation was required " after 450 mg. in 4 days. The patient started walking on the sixth day, and returned to part-time work on the seventh day. A slight recurrence 2 days after stopping cortisone on the 17th day was controlled by rest and neocinchophen only, and the patient had completely recovered in a further 2 weeks. The relapse was associated with rapid recovery, cessation of cortisone, and a too rapid return to normal activities. During cortisone therapy euphoria was evident, giving way to lethargy with a dose below 50 mg. per day. There was some elevation of the blood sugar level and a tendency towards alkalosis. The serum uric acid levels (days) were as follows: 7·0(1); 6·8(3); 5·7(4); 4·32(15). On the fifteenth day " after apparent recovery the serum uric acid level had returned to a high limit of normal at 4·32 ". *H. Coke.*

Cortisone as an Adjunct in the Therapy of Acute Gout. FRIEDLANDER, R. D. (1951). *J. Amer. med. Ass.*, **145**, 11. 11 refs.

A number of published records exist which show that adrenocorticotrophin (ACTH) together with colchicine is efficacious in terminating an acute attack of gout. Very few records of the use of cortisone for this purpose exist, however.

In this well-written paper a case is recorded of acute interval gout in which relief was both rapid and dramatic. Cortisone was not administered in this case until the usual methods of treatment had failed [but there seems to be no doubt from the author's account that relief did not occur spontaneously but was the result of cortisone therapy].

The author puts forward his reasons for believing that cortisone may be a more effective therapeutic agent than ACTH in gout, and suggests also that it may prove in the future to be an important means of preventing this condition from progressing to the tophaceous stage. He points out that although the method by which colchicine effects relief in acute gout is unknown, there is good reason to assume that when given with cortisone or ACTH it exercises a synergistic action and prolongs remissions after the withdrawal of these substances. *W. S. C. Copeman.*

Metabolic and Renal Diabetes Following the Administration of ACTH. A Study of Blood Sugar, Urine Sugar, and Blood Glutathione during the Action of ACTH. HOLTEN, C., and LUNDBAEK, K. (1950). *Scand. J. clin. Lab. Invest.*, **2**, 317. 4 figs, 16 refs.

Two male patients suffering from spondylarthritis ankylopoietica were placed on a standard diet and given Armour ACTH 60-100 mg. daily for a fortnight. The period of investigation was preceded and followed by control periods of one week each. The dose of ACTH was divided into three parts and administered half-an-hour, 5 hrs, and 9½ hrs after breakfast. The patients were confined to bed except for one hour daily.

There was a delayed fall of the blood sugar following the ingestion of carbohydrate giving a curve of the diabetic type. There was also a glycosuria without any rise of fasting or maximum blood sugar values. This suggests that ACTH causes both a metabolic and renal diabetes. Blood glutathione levels were too variable for conclusions to be drawn. *N. Taylor.*

Metabolic Studies with ACTH Protein. [In English.] LUFT, B., SJÖGREN, B., and LI, C. H. (1950). *Acta endocrinol., Kbh.*, **5**, 327. 9 figs, bibl.

In a very detailed paper, the authors have studied the metabolic effects of varying doses of an electrophoretically pure ACTH protein in a male patient suffering from rheumatoid arthritis. There was a clear difference between the effects of a small daily dose of ACTH (3-6 mg.) which affected the salt and water metabolism, and larger doses (up to 50 mg.) which affected not only the salt and water metabolism, but protein-carbohydrate metabolism as well. [This is a valuable paper which should be read in its entirety by those interested.] *N. Taylor.*

Oral Steroid Medication in Rheumatoid Arthritis. FREEMAN, H., PINCUS, G., BACHRACH, S., JOHNSON, C. W., MCCABE, G. E., and MACGILPIN, H. H. (1950). *J. clin. Endocrinol.*, **10**, 1523. 4 figs, 7 refs.

This is a report on treatment by pregnenolone and pregnenolone acetate of 64 cases of chronic rheumatoid arthritis with marked anatomical and functional disability. The definition, classification, and degree of response were estimated according to the standards of Steinbrocker (*J. Amer. med. Ass.*, 1949, **140**, 659). The advantages of administration by the oral route were considered, and no secondary or physiological side-effects of this steroid were found. A placebo control treatment was administered for the first 2 weeks, during which only three patients reported mild improvement. After therapy the improvement was evident in 2 weeks and increased as medication was maintained. Major improvement occurred in 24 patients (38 per cent.), eleven

of whom had been moderately or totally incapacitated initially. The average length of treatment was 12·3 weeks. In half the cases the sedimentation rate returned to normal, and there was a decrease of 28 per cent. in the average level of eosinophiles. 26 patients (41 per cent.) showed improvement of lesser degree, eleven of whom had been seriously incapacitated in the first place. The third group of fourteen patients (21 per cent.) showed no improvement; these showed much less change in the sedimentation rate and none in the eosinophile level. Thus the greater improvement occurred with the less severe cases of initial anatomical and functional disability, and in the younger age group (20-39 years). Maintenance of improvement after cessation of therapy was assessed in eighteen cases showing major improvement, and it was evident that the longer the treatment the longer the improvement was maintained. Some cases given control tablets showed no significant difference in comparison with those who received nothing after the cessation of successful therapy, and this was considered to obviate psychological factors. The optimal dosage was considered to be 500 mg. daily for at least 8 weeks, the minimum average daily maintenance dose being 400 mg.

The authors conclude that "pregnenolone can be regarded as an aid in the treatment of rheumatoid arthritis, is less expensive than ACTH or cortisone, is easier for the patient, and has no secondary effects".

H. Coke.

Pregnenolone in Rheumatoid Arthritis. DORDICK, J. R., ERHLICH, M. E., ALEXANDER, S., and KISSIN, M. (1951). *New Engl. J. Med.*, **244**, 324. 10 refs.

Twenty-five patients with rheumatoid arthritis and eight with other diseases were given pregnenolone, either orally or intramuscularly, or by both routes. Dosage varied from 300 to 1,000 mg. daily. The patients were observed for an average of 14 weeks; two with rheumatoid arthritis improved and four had slight questionable improvement, but in all others no significant benefits were obtained. Two patients developed headache, which disappeared with reduction of dosage. After the use of intramuscular administration, painful local induration occurred regularly; sterile abscesses formed, requiring drainage, in two cases.—[*Authors' summary.*]

Therapeutic Suppression of Tissue Reactivity. II. Effect of Aminopterin in Rheumatoid Arthritis and Psoriasis. GUBNER, R., AUGUST, S., and GINSBERG, V. (1951). *Amer. J. med. Sci.*, **221**, 176. 1 fig., 24 refs.

The scarcity of cortisone and ACTH, together with the reports of untoward side-effects following their prolonged administration, has stimulated investigation of a large number of steroids which might be thought to have somewhat similar properties. On the assumption that the beneficial effect of cortisone in arthritis may lie in the power of inhibiting connective-tissue proliferation, the authors have used the folic acid antagonist 4-aminopteroylglutamic acid (aminopterin) in the treatment of seven cases of rheumatoid arthritis, and one of rheumatic fever. The daily dosage employed was 1 to 2 mg., the total ranging from a minimum of 6 mg. to 40 mg. over periods varying from 6 to 21 days. It was found that although aminopterin has no analgesic effect it produced significant clinical amelioration in seven of the eight cases treated. There was no evidence, however, of any effect upon the course of the disease as indicated by the erythrocyte sedimentation rate, serum protein level, or leucocyte changes. As is often the case also with cortisone therapy, withdrawal symptoms in the form of acute exacerbation of the arthritic process for several weeks occurred.

It was not thought that the clinical effect of aminopterin is medicated through the pituitary or adrenal routes, but that it is due to direct inhibition of mesenchyme and, to a lesser extent, epithelial tissues. The toxic effects of aminopterin unfortunately appear to place a limitation on its practical use as a therapeutic agent.

W. S. C. Copeman.

Salicylate, Gentisate, and Circulating Eosinophils. MEADE, B. W., and SMITH, M. J. H. (1951). *Lancet*, **1**, 773. 14 refs.

The effect of single doses of sodium salicylate and sodium gentisate on the circulating eosinophils has been studied in normal healthy subjects. No significant depression was observed with plasma-salicylate concentrations up to 38 mg. per 100 ml. and plasma-gentisate concentrations up to 35 mg. per 100 ml.—[*Authors' summary.*]

Combined Administration of Desoxycorticosterone Acetate and Ascorbic Acid. I. Clinical Results in Rheumatoid Arthritis and Laboratory Studies. MCKENDRY, J. B. R., SCHAFFENBURG, C. A., and MCCULLAGH, E. P. (1951). *Arch. intern. Med.*, **87**, 190. 35 refs.

Combined treatment was given to 23 patients suffering from rheumatoid arthritis. There were no controls. Of the sixteen patients who received more than two treatments, nine reported definite improvement within a few days.

D. P. Nicholson.

Combined Administration of Desoxycorticosterone Acetate and Ascorbic Acid. II. Experimental Observations. SCHAFFENBURG, C. A., MCKENDRY, J. B. R., and MCCULLAGH, E. P. (1951). *Arch. intern. Med.*, **87**, 199. 26 refs.

The effects of the combined administration of deoxycortone acetate and ascorbic acid to mice were studied by means of the cold test, egg-white reaction, and formaldehyde-induced arthritis. It is concluded from the results of these experiments that this combined administration has no cortisone-like activity. It showed no effect in protecting mice against formaldehyde-induced arthritis, in contrast to the previously reported work of Brownlee.

D. P. Nicholson.

Acetylsalicylic Acid and Urinary Excretion of Adrenocortical Steroids. VAN CAUWENBERGE, H., and HEUGSHEM, C. (1951). *Lancet*, **1**, 771. 7 refs.

This is a preliminary report on the study of the effect of acetylsalicylic steroids in eight patients suffering from "collagen" diseases—rheumatic fever, rheumatoid arthritis, ankylosing spondylitis, and fibrositis with endarteritis. Before treatment all patients had a low output of reducing steroids. With salicylates excretion was markedly raised, but fell at once on cessation of treatment. An increased output of reducing steroids was associated with clinical improvement. No regular variation was found in the excretion of 17-ketosteroids

during salicylate therapy, and variations in excretion were not correlated with the clinical course.

The results suggest a relation between salicylate and cortisone therapy. *H. F. Turney.*

Cortisone in Sydenham's Chorea. Report of Two Cases. ARONSON, N., DOUGLAS, H. S., and LEWIS, J. M. (1951). *J. Amer. med. Ass.*, **145**, 30. 2 figs, 10 refs.

In view of the traditional belief that chorea is a manifestation of rheumatic fever, cortisone was administered by these observers to two children suffering from acute chorea. In neither case was there any favourable response. The total amount of cortisone administered was 0·975 g. over a 14-day period in one case, and 2·175 g. over a 20-day period in the other. In one of these cases nearly 1 g. adrenocorticotrophin was given later over a period of nine days, and this was also without significant effect upon the course of the disease. *W. S. C. Copeman.*

Early Experience in the Treatment of Progressive Rheumatic Carditis with Adrenocorticotrophin and Cortisone. (Première expérience de traitement des cardites rhumatismales évolutives par l'ACTH et las cortisone.) COSTE, F., TURPIN, R., DELBARRE, F., TOURNEUR, R., and OURY, M. (1950). *Bull. Soc. méd. Hôp. Paris*, **66**, 1577. 12 figs, 9 refs.

Details are given of the treatment with adrenocorticotrophin (ACTH) and cortisone of fifteen children with acute rheumatic fever. In most cases ACTH was used initially, since it was considered to act more rapidly than cortisone. Administration of the hormone was continued for 3 to 6 weeks in dosages varying with the potency of the preparation. One patient died and the first five had such small doses that the effects of treatment could not be assessed accurately. In the other cases there was a rapid regression of general signs and symptoms. Pericarditis subsided rapidly and there appeared to be definite though slower improvement in cases of myocardial or endocardial involvement. Established valvular lesions were unaffected. Some complications occurred, of which oedema and oliguria were the most serious. Relapses occurred when treatment was stopped suddenly or too early.

From a careful study of these cases the authors conclude that ACTH and cortisone have beneficial effects on the cardiac lesions in the acute stage of rheumatic fever but recommend further prolonged and statistical investigations to determine whether permanent cardiac damage is preventable by early hormone therapy. *Kathleen M. Lawther.*

Effects of Pituitary Adrenocorticotropic Hormone (ACTH) on Rheumatic Fever and Rheumatic Carditis. MASSELL, B. F., and WARREN, J. E. (1950). *J. Amer. med. Ass.*, **144**, 1335. 2 figs, 14 refs.

The clinical effect of pituitary adrenocorticotropic hormone (ACTH) has been observed in twenty patients with active rheumatic fever. In many patients the rheumatic process was severe, and most of them had active carditis. The initial response of fever and joint involvement was especially impressive, but pericarditis, subcutaneous nodules and other rheumatic manifestations also frequently disappeared during hormone therapy. Withdrawal reactions with clinical manifestations of rheumatic fever or with only elevation of the sedimentation rate were sometimes observed when hormone therapy was completed. In most but not all such instances these signs of rheumatic activity again subsided spontaneously over varying periods of time without any further treatment.

Of two patients with chorea, one showed striking improvement in association with pituitary adrenocorticotropic hormone therapy; the other failed to respond to a 10-day period of treatment with the hormone in large doses. Treatment has been completed in seventeen of the eighteen patients with rheumatic manifestations other than chorea. Three of these cases must be considered therapeutic failures. Although the total duration of active rheumatic fever varied greatly in the remaining fourteen patients, it was our impression that, on the whole, recovery took place sooner than it would have without treatment.

The apparent response of pericarditis congestive failure and subcutaneous nodules to pituitary adrenocorticotropic hormone in a number of patients and the complete disappearance in two patients of all significant murmurs strongly suggest that in some instances active carditis may be favourably influenced by hormone treatment. Also, there are hopeful indications that if therapy is begun early in an attack of rheumatic fever cardiac damage may be lessened or prevented.

The only harmful reactions definitely attributable to pituitary adrenocorticotropic hormone in this series were retention of fluids with aggravation of congestive heart failure and, in one instance, serious mental depression. It is possible that in one patient with longstanding, low-grade rheumatic fever the degree of rheumatic activity was greater after discontinuation than before the administration of the hormone. One instance of fatal jugular thrombophlebitis was encountered, but as yet there is no definite reason to attribute this complication to pituitary adrenocorticotropic hormone therapy.

The mechanism of hormonal influences in rheumatic fever is not yet understood.—[*Authors' summary.*]

Effect of Pituitary Adrenocorticotropic Hormone (ACTH) in Acute Rheumatic Carditis. WILSON, M. G., and HELPER, H. N. (1951). *J. Amer. med. Ass.*, **145**, 133. 4 figs, 7 refs.

This is a report of the trial of adrenocorticotropic hormone (ACTH) in eleven consecutive cases of acute rheumatic carditis, in patients aged 6 to 18 years. Compared with previous experience ACTH had a notable effect on the course, duration, and resultant state. From their experience the authors suggest that the rheumatic process is reversible. Dosage used was 80 to 100 mg. every 6 hours for 3 days, and then 40 to 60 mg. daily for 4 days. Insufficient dosage may result in a relapse after cessation of treatment. Signs and symptoms of carditis subsided in 3 to 7 days, and patients were ambulant in 2 to 4 weeks. *David Nicholson.*

The Effect of Some Steroids (Testosterone Propionate, Desoxycorticosterone Acetate and Ascorbic Acid, and 21-Acetoxy-Δ-5-pregnenolone ("Artisone Acetate") in Rheumatoid Arthritis. MARGOLIS, H. M., and CAPLAN, P. S. (1951). *Ann. intern. Med.*, **34**, 61. 6 refs.

This report summarizes in general terms the experience of the authors in the treatment of 64 cases of the "typical clinical picture of generalized rheumatoid arthritis"; 31 patients were treated with large doses of testosterone

propionate, 28 patients with deoxycortone (desoxycorticosterone) acetate and ascorbic acid by the technique of Lewin and Wassén, and five patients with " artisone " (21-acetoxy-Δ-5-pregnenolone). Tables of results are given. The authors conclude that none of these three individual methods produced any specific beneficial effect. Assessment was based in general terms on subjective changes, and objectively on measurement of erythrocyte sedimentation rate and studies of blood. Controls were included. Subjective systemic improvement as a result of testosterone therapy was the only benefit noted in 61 per cent. of this group. Three patients given artisone were subsequently treated with adrenocorticotrophin (ACTH) with the usual beneficial results. *Harry Coke.*

The Synergistic Action of *para*Aminobenzoic Acid and Cortisone in the Treatment of Rheumatoid Arthritis. WIESEL, L. L., BARRITT, A. D., and STUMPE, W. M. (1950). *Brooklyn Hosp. J.*, **8**, 148. 11 refs.

The authors treated three cases of severe or moderately severe rheumatoid arthritis with cortisone, the efficacy of the treatment being judged by assessment of joint pain and swelling. Cortisone was given in dosage sufficient to reduce these to a minimum. Reduction of the dose of cortisone to 25 mg. daily produced a relapse in all three cases. When, however, a daily dose of 12 g. sodium *p*-aminobenzoate was added to this small dose of cortisone, joint pain and swelling abated once more. Control treatment with *p*-aminobenzoic acid alone had no effect on the arthritis. *G. Loewi.*

Oral Use of Cortisone Acetate. BOLAND, E. W., and HEADLEY, N. E. (1951). *J. Amer. med. Ass.*, **145**, 8. 10 refs.

It has been reported in several recent papers that cortisone can be given by mouth and will, in most cases, produce results in rheumatoid arthritis as striking as those obtained by intramuscular injection. It is also generally agreed that the dosage needed by the former route approximates to that usually given by the latter.

A report is given of the treatment of 23 patients with chronic rheumatoid arthritis by oral administration of cortisone, the study being designed to compare its effectiveness with that of intramuscular administration.

In all but one of these cases the oral route was found to be highly effective in suppressing the activity of the disease and controlling the rheumatic manifestations. It seemed in general that the therapeutic effects produced by oral administration occurred more rapidly and disappeared more rapidly than was the case when injections were used. In about half of the series larger amounts were needed to produce equal maintenance effects, the oral dose ranging from one-fifth to one-third more than the injected dose. No gastro-intestinal symptoms occurred as a result of oral administration, but the period of observation in this series was too short for any conclusions to be drawn as regards the safety of prolonged administration.

W. S. C. Copeman.

Oral Steroid Medication in Rheumatoid Arthritis. FREEMAN, H., PINCUS, G., BACHRACH, S., JOHNSON, C. W., MCCABE, G. E., and MACGILPIN, H. H. (1950). *J. clin. Endocrinol.*, **10**, 1523. 4 figs, 7 refs.

An analysis is presented of the results of treating seventeen men and 47 women suffering from rheumatoid arthritis with large doses (500 mg. daily) of pregnenolone by mouth. Placebo treatment was first given for 2 weeks, and three patients who improved during this period were excluded from the series. Of the remainder, 24 (38 per cent.) showed major improvement as evidenced by diminution of pain, increase in joint mobility, decrease in swelling, and increase in strength. Duration of treatment was from 3 to 30 weeks, with a mean of 12·3 weeks. In half the cases the erythrocyte sedimentation rate (E.S.R.) fell to normal, the mean figure after treatment being 64 per cent. of the original value. The average fall in eosinophil count in this group was 28 per cent. In 26 cases (42 per cent.) there was wild and less striking improvement. Fall in E.S.R. was less, the mean value after treatment being 74 per cent. of the pre-treatment level. Eosinophil count did not fall in this group. No improvement as regards either symptoms or E.S.R. occurred in fourteen cases. Relapse was usual after cessation of treatment. The authors believe that maximal improvement was obtained with 500 mg. daily; larger doses brought no further improvement. No constant untoward effects were noted. Oral medication is considered preferable to injection. Injected crystals may remain for weeks undissolved in the muscles.

C. L. Cope.

The Influence of Artificial Pyrexia and of Progesterone on the Adrenal Cortex in Chronic Rheumatism. (Influenza della piressia artificiale e del progesterone sul corticosurrene nel reumatismo cronico.) LUCHERINI, T., CECCHI, E., and VOLPICELLI, M. (1950). *Minerva med., Torino*, **2**, 483. 3 figs, bibl.

A survey of the literature on adrenocorticotrophin stimulated the authors to give to 27 patients with rheumatoid arthritis or with osteo-arthritis one of three kinds of treatment: production of artificial pyrexia by stock vaccine or administration of deoxycortone or progesterone, the last two being combined with ascorbic acid administration. Pyrexia produced a fall of eosinophil count and a corresponding increase in the ratio of uric acid to creatinine in the urine of three patients out of a group of ten. The second form of treatment, given in twelve cases, produced a fall in eosinophil count in two and a rise in the ratio of uric acid to creatinine in eight. Progesterone (one dose of 100 mg.) was given to only four patients, but clinical changes were not significant. Perhaps the changes observed are due to stimulation of both the pituitary and the adrenal glands.

E. Neumark.

Effects of Cortisone on Acute Disseminated Lupus Erythematosus. BRUNSTING, L. A., SLOCUMB, C. H., and DIDCOCT, J. W. (1951). *Arch. Derm. Syph., Chicago*, **63**, 29. 4 figs, 21 refs.

Thorough studies were made of seven cases, in women, of acute disseminated lupus erythematosus treated with cortisone and adrenocorticotrophin (ACTH). The symptoms improved strikingly and rapidly, though high doses of cortisone (200 mg. daily) had sometimes to be used. The usual dose was 100 mg. daily. Relapse occurred at varying intervals after stopping treatment. Laboratory findings were either only slightly improved or were unchanged by the treatment. Wound healing was unaffected. The patients were euphoric during treatment and sometimes became temporarily unbalanced emotionally. Cessation of treatment was sometimes

followed by feelings of depression and weakness. Rounding of the face, acne, and hirsuties disappeared after cessation of treatment; striae persisted. Salt and water retention was marked and, in one case, led to fatal oedema. Signs of a supervening acute infection could be dangerously masked. Cortisone and ACTH are dangerous substances, which should be used only in the presence of facilities for full laboratory control.

E. Lipman Cohen.

Occurrence of Convulsive Seizures during Treatment of Asthma with Cortisone Acetate. LOWELL, F. C., FRANKLIN, W., BEALE, H. D., and SCHILLER, I. W. (1951). *New Engl. J. Med.*, **244**, 49. 4 refs.

The authors record the occurrence of epileptiform convulsions in a patient with chronic asthma under treatment with cortisone. Cortisone was administered intramuscularly in 50-mg. doses, two being given on the first day of treatment and four (50 mg. 6-hourly) on subsequent days. The asthma began to improve on the 4th day and from that time the patient remained free from respiratory symptoms. On the 11th day of treatment he complained of headache which persisted during the next day, when he had four epileptiform fits. No cortisone was given on that day but 50 mg. was administered on the 13th day, and 100 mg. subsequently without fits recurring. An electroencephalogram (EEG) taken two days after the fits showed some rhythmic slow activity with no focal abnormality. A month later, when the dose of cortisone was being gradually decreased and the patient was receiving 50 mg. daily, lid-lag and tremor of the hands were observed; these symptoms disappeared and the asthma recurred 3 weeks after cortisone was stopped. The EEG was normal 3 months later.

Epileptiform seizures have previously been described as occurring during adrenocorticotrophic hormone therapy but not during treatment with cortisone. The fits were attributed to cortisone because the patient had never previously had convulsions and there was no family history of epilepsy. During the 10 days before the fits occurred the patient had gained 5 lb. (2·26 kg.) in weight; the authors suggest that this was due to retention of salt and water and may have been responsible for the seizures.

R. S. Bruce Pearson.

Mild Cushing's Syndrome due to Aspirin. COCHRAN, J. B., WATSON, R. D., and REID, J. (1950). *Brit. med. J.*, **2**, 1411. 3 figs, 6 refs.

The case is reported of a girl aged 13 years suffering from her third attack of rheumatic fever with cardiac involvement and a temperature of 104° F. (40° C.). She was treated with aspirin in doses up to 5 g. daily. During treatment her face became rounded and "puffy" but not oedematous, acne appeared on the forehead, chest, shoulders, and back, and she became morose. The urine contained a reducing sugar and there was a mild diabetic type of blood sugar tolerance. Water and chlorides were retained and there was a negative nitrogen balance. The albumin-globulin ratio returned to normal from its original reversed state and plasma fibrinogen level also fell to normal.

The authors regard these symptoms as manifestations of mild Cushing's syndrome which gradually subsided as the aspirin dosage was reduced. They consider them to be the result of aspirin treatment, compare them with the similar results obtained with cortisone, and discuss possible modes of action.

A. C. Crooke.

The Treatment of Diseases of Dysreaction (Rheumatoid Arthritis, Asthma) with Nitrogen Mustard (Le traitement des maladies de dysréaction (arthrite rhumatoïde, asthme) par les moutardes azotées.) JIMÉNEZ-DÍAZ, C., MERCHANTE, A., PERIANES, J., LOPEZ, E., and PUIGLEAL, J. (1950). *Helv. med. Acta*, **17**, 583. 2 figs, 44 refs.

It is fortunate, in the opinion of the authors, that many disease processes can be favourably influenced without much knowledge of their aetiology. In this connexion they make a brief reference to the dramatic effects of cortisone and adrenocorticotrophin (ACTH) in rheumatoid arthritis, as demonstrated by Hench and his collaborators; they also refer to the work of Klemperer and others on the "collagen diseases" and to Selye's theory of "diseases of adaptation". Antigen-antibody reaction in the tissues is discussed, as well as the possible precipitation in the ground substance of "mucopolysaccharide acid". Some workers have claimed that cortisone and ACTH increase the amount of circulating γ-globulin and of antibodies, while others have been unable to confirm these results; there is general agreement, however, that these hormones decrease the number of circulating eosinophils.

Cortisone and ACTH are difficult to produce and their prolonged use may result in unpleasant side-effects. The authors were encoured in their decision to use nitrogen mustard (HN^3) by the fact that these drugs produce an eosinopenia comparable to that caused by the above hormones; their over-all effect was to produce all the phenomena of the "alarm reaction". Although extirpation of the adrenals does not abolish this reaction, hypertrophy of these glands (stimulation by nitrogen mustard) can be demonstrated at necropsy. The excretion of 17-ketosteroids in the urine is increased. Brief histories are given of fourteen cases of rheumatoid arthritis treated with HN^3 intravenously (0·1 mg. per kg. body weight, on alternate days, to a total of four or five injections). Although these cases were of long standing, with severe manifestations, the beneficial effects were not in doubt; in nine of them they were remarkable. Swellings and effusions largely disappeared and the power of locomotion was restored to bedridden patients. One month later, all cases were reassessed. In only three of them was there partial relapse; in the rest improvement was maintained. Blood counts showed a constant fall in circulating leucocytes, mainly in lymphocytes and eosinophils; leucopenia tended to increase a fortnight after cessation of treatment and reached its peak in those cases given more than 15 mg., thrombocytopenia frequently appearing in these cases. Although, in general, side-effects were not alarming, the authors consider it wiser to limit the number of injections to three (4 to 5 mg. each); with this dosage no complications need be feared. The erythrocyte sedimentation rate was unaffected; excretion of uric acid in the urine fell at first but subsequently rose, and that of 17-ketosteroids was initially increased and later returned to its original level.

Six cases of bronchial asthma have been treated so far (five of them in status asthmaticus). The effects were comparable to those reported from the use of ACTH, and clinical improvement appeared to keep step with the reduction in circulating eosinophils. The authors have begun to treat other cases of "dysreaction" (dermatomyositis, sclerodermia, psoriasis), but results are not yet available. Though the mode of action of HN^3 is still

obscure they think that it is similar to that of ACTH and cortisone; they draw attention to the anti-mitotic effect of ACTH and HN^2. *D. Preiskel.*

The Effect of Cortisone upon the Experimental Cardiovascular and Renal Lesions produced by Anaphylactic Hypersensitivity. RICH, A. R., BERTHRONG, M., and BENNETT, I. L. (1950). *Bull. Johns Hopk. Hosp.*, **87**, 549. 3 figs, 10 refs.

Having confirmed the fact that in sensitized animals treated with adrenocorticotrophin (ACTH) the incidence of cardiovascular lesions decreased, the authors describe a similar experiment. Rabbits were treated with cortisone and sensitized by intravenous horse serum. Among many interesting observations it was found that cortisone had little effect either on skin sensitization or on serum antibody levels. The incidence of cardiovascular lesions was much lower in the treated animals, the figures being practically identical with those obtained in a similar experiment with ACTH. The proliferative glomerular lesions seen in sensitized animals were completely absent but a haemorrhagic lesion with focal glomerular necrosis was observed in many instances. It resembled the change seen in cases of diabetes mellitus and lupus erythematosus, but it is noteworthy that it was never observed in the animals treated with ACTH. The spleen contained foci of extramedullary blood formation and the liver excess of glycogen. *G. J. Cunningham.*

Use of Pituitary Adrenocorticotropic Hormone (ACTH) and Cortisone in Lymphomas and Leukemias. PEARSON, O. H., and ELIEL, L. P. (1950). *J. Amer. med. Ass.*, **144**, 1349. 15 refs.

This is a report on the results of treatment of seventy patients suffering from various types of neoplastic disease with pituitary adrenocorticotrophic hormone (ACTH) and cortisone acetate. Eight patients with chronic lymphatic leukaemia received 100 to 200 mg. ACTH or cortisone acetate per day for 18 days to 3 months. All patients showed appreciable shrinkage of large lymph nodes, liver, and spleen during treatment. Relapse occurred at varying intervals after treatment was stopped, and in some it occurred slowly in spite of continued treatment. Subsequent courses of treatment proved beneficial in six cases. Some patients showed a rise in haemoglobin value and erythrocyte count in the blood during treatment. In all patients there was a transitory rise in the leucocyte count followed by a fall to below pre-treatment levels. In no patient was there alteration in the differential count or improvement in the bone-marrow picture.

Six patients with lymphosarcoma received ACTH or cortisone daily for 9 to 52 days. Definite shrinkage of tumour masses was observed in all cases: four patients were in the terminal stages of the disease when treatment was begun. They died during treatment in spite of transient improvement in the local tumours. In some patients remissions lasted for 3 months after stopping treatment, and subsequent treatment failed to reveal any sign of refractoriness to the active substance.

Of thirty cases of acute leukaemia receiving one of the drugs, thirteen showed " a good clinical and hematological remission " and eight did not respond. Monocytic leukaemia appears to be unaffected by these hormones. In acute myeloid or acute lymphatic leukaemia remissions were of short duration and refractoriness to treatment rapidly developed. Of six patients with Hodgkin's disease, four showed slight shrinkage of enlarged lymph nodes and spleen; lasting benefit was not obtained. A patient with plasma-cell myeloma obtained marked clinical benefit from ACTH. The bone-marrow picture remained unaltered. When treatment was stopped there was recurrence of symptoms within 24 hours.

[This paper provides very few details of treatment. Thus it is not stated which patients received cortisone and which received ACTH, and nothing is said of the relative merits of these hormones in the treatment of the various forms of reticulosis.] *A. Brown.*

Effects of Cortisone and ACTH Therapy on Eosinophils of the Bone Marrow and Blood. ROSENTHAL, R. L., WALD, N., YAGER, A., and LITWINS, J. (1950). *Proc. Soc. exp. Biol., N.Y.*, **75**, 740. 5 refs.

Eosinophil counts were performed on blood and bone marrow of seven patients before and during either cortisone or ACTH therapy. At a time of marked diminution in the eosinophils of the peripheral blood, the eosinophilic cells of the bone marrow were not decreased.—[*Authors' summary.*]

Simulated Adreno-cortical Activity during Pregnancy in an Addisonian Patient. JAILER, J. W., and KNOWLTON, A. I. (1950). *J. clin. Invest.*, **29**, 1430. 3 figs, 15 refs.

It has been shown that normal pregnancy is associated with a rise in the excretion of glucocorticoids and 17-ketosteroids, an indication of increased maternal adrenal cortical activity. In this paper the authors describe the case of a woman with adrenal insufficiency who was under frequent observation at the Presbyterian Hospital, New York, during pregnancy. The course of an earlier successful pregnancy in the same patient has been reported previously (Knowlton *et al.*, *J. clin. Endocrinol.*, 1949, **9**, 514). Satisfactory control of the adrenal disease during the earlier part of pregnancy was achieved by the implantation of deoxycortone acetate (DCA) pellets, together with administration of sodium chloride by mouth, and from the seventh months onwards 2 mg. DCA was injected daily. The patient was delivered, 19 days prematurely, of a healthy infant and during the 4 months following remained in satisfactory health. The output of gonadotrophin, oestrogen, and pregnanediol was normal throughout this pregnancy. From the sixth week onwards the 17-ketosteroid excretion was markedly increased (from 4·5 to 9·9 mg. daily compared to 1 mg. daily one year before the onset of pregnancy). During the week following delivery steroid excretion fell gradually, and thereafter it was characteristic of Addison's disease. The output of neutral reducing lipids was within the range found in normal pregnancy, an unexpected finding in a patient with adrenal insufficiency.

A marked fall in eosinophil count occurred in the pregnant patient on administration of adrenocorticotrophin (ACTH); 10 days post partum this test was completely negative, even with large doses of ACTH given on five successive days. This finding does not support the possibility of the presence of residual adrenal tissue capable of responding to the stimulus of pregnancy. The output of 17-ketosteroids of the new-born infant was too small to account for the increase in maternal excretion. Preliminary tests revealed ACTH-like activity in acetone-dried placental tissue from this case, suggesting that the

placenta was the source of adrenal cortical hormones, or close analogues, during pregnancy. *Nancy Gough.*

Clinical Trials of A.C.T.H. in Haemolytic Anemia. DAVIDSON, L. S. P., DUTHIE, J. J. R., GIRDWOOD, R. H., and SINCLAIR, R. J. G. (1951). *Brit. med. J.*, **1**, 657. 1 fig., 4 refs.

The authors have treated three cases of haemolytic anaemia with ACTH in a dose of 100 mg. daily for 10 days. ACTH rapidly controlled the haemolytic phenomena in one case of acquired haemolytic anaemia; the symptoms have not recurred, and the Coombs test was negative and an abnormal antibody no longer present 8 months after treatment was started, although both remained positive for some time after symptoms had completely ceased. In two cases of congenital haemolytic anaemia there was little or no response to the administration of ACTH in similar doses. The authors suggest that the control of haemolysis by ACTH in acquired haemolytic anaemia is not due to suppression of the production of abnormal antibodies. *Janet Vaughan.*

Hemorrhagic Diathesis with Ascorbic Acid Deficiency During Administration of Anterior Pituitary Corticotropic Hormone (ACTH). STEFANINI, M., and ROSENTHAL, M. C. (1950). *Proc. Soc. exp. Biol., N.Y.*, **75**, 806. 12 refs.

Two patients developed haemorrhagic manifestations presumably due to ascorbic acid deficiency while receiving high doses of adrenocorticotrophic hormone (ACTH). One received 2·7 g. ACTH, which was twice as potent as a certain standard " LA-1-A ", in 125 days. The other patient received 28 mg. of an ACTH preparation, 25 to 30 times as potent as LA-1-A, in 9 days. Petechiae appeared in the first patient on the 115th day and in the second on the 9th day. In both, large petechiae were produced on pricking the skin. On the administration of ascorbic acid no further haemorrhagic manifestations occurred.

The diagnosis was based on: (1) haemorrhagic manifestations with only moderate disturbance of other factors of haemostasis, especially following minimal trauma to the skin; (2) low plasma ascorbic acid level (0·17 and 0·4 mg. per 100 ml.) and low urinary excretion of ascorbic acid; (3) low plasma ascorbic acid tolerance curve (in the one case where this was performed) after intravenous injection of 1 g.; (4) therapeutic effect of ascorbic acid on skin haemorrhages.

It is pointed out that ascorbic acid deficiency is probably not common in the course of ACTH therapy but should be considered if haemorrhagic signs appear during prolonged administration of this hormone.

Norval Taylor.

Effect of ACTH and Suprarenal Extract on the Bone Marrow. YOFFEY, J. M., METCALF, W. K., HERDAN, G., and NAIRN, V. (1951). *Brit. med. J.*, **1**, 660. 43 refs.

The authors have studied the effect of ACTH and adrenal cortical extract on the bone marrow of guinea-pigs. A quantitative technique to determine the number of nucleated cells in the marrow is described. This was applied to 25 normal guinea-pigs, to nine guinea-pigs who had received 0·1 ml. " eschatin " per 100 g. body weight intraperitoneally, and to ten guinea-pigs who had received 1 mg. ACTH per 100 g. intraperitoneally. The normal guinea-pig marrow contained an average of 1,236,000 nucleated cells per c.mm., of which 14,800 were lymphocytes. There was no demonstrable increase of damaged cells in the marrow 6 hours after giving either ACTH or the adrenal extract, but there was a statistically significant increase in the lymphocyte content after giving the latter, and an increase almost reaching the significant level in the case of ACTH. It is suggested that increased uptake of lymphocytes from the blood by the bone marrow may possibly be a contributory factor in the lymphopenia which may follow the administration of ACTH or steroid hormones. *Janet Vaughan.*

Effect of Commercial Cortisone Acetate Suspension on Capillary Permeability. MENKIN, V. (1951). *Amer. J. Physiol.*, **164**, 294. 1 fig, 11 refs.

Commercial cortisone acetate suspension injected intracutaneously into rabbits in amounts ranging from 0·5 to 2·0 mg. produced increased capillary permeability at the site of injection. By injecting in a similar way comparable amounts of different cortical extracts or substances used for the suspension of these preparations, the author had demonstrated that the increase in capillary permeability was due solely to the material used as the vehicle for the cortisone, probably some type of alcohol. Adrenocorticotrophic hormone (ACTH) produced no such effect. Cortisone acetate, free from any alcohol or vehicle, failed to increase capillary permeability when suspended in saline. This effect on the capillaries may possibly help to elucidate the action of cortisone acetate suspension in arthritic conditions and this additional variable, the author believes, will have to be taken into account in a number of clinical studies.

A. I. Suchett-Kaye.

Hypercoagulability of the Blood associated with ACTH and Cortisone Therapy. COSGRIFF, S. W., DIEFENBACH, A. F., and VOGT, W. (1950). *Amer. J. Med.*, **9**, 752. 2 figs, 6 refs.

This study was prompted by the observation of several thrombo-embolic complications, including two fatal cases of pulmonary embolism, in patients receiving cortisone or adrenocorticotrophin (ACTH). In eight out of ten patients the venous clotting time was considerably shortened during the administration of cortisone or ACTH, and in four out of six cases the "heparin retarded" venous clotting time was similarly reduced. No consistently significant changes were found in the prothrombin time, blood content of fibrinogen B, or protamine titration. It is concluded that both ACTH and cortisone frequently produce a hypercoagulable state of the blood, the mechanism of which is unexplained.

C. Bruce Perry.

17-Ketosteroid Excretion in the Diagnosis of Endocrine Dysfunction. BUTT, W. R., MASON, A. S., and MORRIS, C. J. O. R. (1950). *Lancet*, **2**, 894. 2 figs, 23 refs.

Working at the London Hospital and using the polarographic method of determination, the authors have studied the 17-ketosteroid excretion of 235 patients with endocrine dysfunction.

Group 1 consisted of patients with adrenal cortical hyperfunction, and virilism or obesity resembling that of Cushing's syndrome. Usually, but not invariably, an increase occurred in 17-ketosteroid output corresponding to the degree of virilism; simple hirsutism alone did not appear to be related to increased output. In conditions resembling Cushing's syndrome, however, there was no

relation between the severity of the disturbance and the 17-ketosteroid excretion. Group 2 consisted of patients suffering from cortical failure, in whom a decreased excretion of 17-ketosteroids would be expected. In seven verified cases of Addison's disease and in nine cases of primary pituitary failure a strikingly low output of 17-ketosteroid was observed (less than 3 mg. in 24 hours); in primary testicular failure there was a far less marked fall in 17-ketosteroid excretion.

In various miscellaneous endocrine disorders, dwarfism, pituitary tumours, and thyrotoxicosis, the androgen output could not be related to the clinical findings.

The authors point out that factors other than endocrine disturbances, such as age, chronic illness, malnutrition, and impairment of liver function influence the 17-ketosteroid excretion, thereby reducing its value as a diagnostic test. The test is reliable in adrenal failure, either primary or due to pituitary failure, and of some value as an indication of adrenal hyperfunction in cases of virilism; in other endocrine diseases no reliance can be placed upon it as a diagnostic aid. *Nancy Gough.*

The Effects of Cortisone on the Course of Acute Glomerulonephritis. Report of a Case. BURNETT, C. H., GREER, M. A., BURROWS, B. A., SISSON, J. H., RELMAN, A. S., WEINSTEIN, L. A., and COLBURN, C. G. (1950). *New Engl. J. Med.*, **243**, 1028. 1 fig., 10 refs.

A case of acute glomerulonephritis was studied for 43 days. During this period, 200 mg. cortisone was administered daily for 12 days. The signs of nephritis at that time were haematuria, albuminuria, and the presence of urinary casts. While the patient was on cortisone there was a rise in temperature and increase in protein and erythrocytes in the urine, probably a non-specific effect. It was considered doubtful whether cortisone had been of benefit. *G. Loewi.*

Cortical Steroids in Treatment of Cancer. Observations on Effects of Pituitary Adrenocorticotropic Hormone (ACTH) and Cortisone in Far Advanced Cases. TAYLOR, S. G., AYER, J. P., and MORRIS, R. S. (1950). *J. Amer. med. Ass.*, **144**, 1058. 6 figs, 16 refs.

The effect of pituitary adrenocorticotrophin (100 to 200 mg. daily for individual periods of 2 weeks to 3½ months) and of cortisone (100 to 300 mg. daily for similar periods) was studied in 26 cases of far advanced malignant disease. Most patients showed marked temporary improvement in general condition. The improved state lasted until side-effects from long-continued therapy ensued or complications produced by the progress of the neoplastic disease developed. The side-effects included disturbances of electrolyte balance (such as sodium retention or potassium loss), decrease in glucose tolerance, mental changes, altered response to infection, pigment disturbances, sexual disturbances, and development of Cushing's syndrome. Temporary regression of neoplastic lesions was observed in three cases of Hodgkin's disease, five cases of lymphosarcoma, and one case of chronic lymphatic leukaemia; a doubtful regression of angio-endothelioma (Ewing's sarcoma) occurred with ACTH. In cases of carcinoma, acute leukaemia, myelogenous leukaemia, and melanoma the disease was not controlled. Because of the physiological alterations produced by these hormones when given in large doses, however, repeated or prolonged therapy is ill-advised. *L. A. Elson.*

Effects of Cortisone in Certain Neuromuscular Disorders. SHY, G. M., BRENDLER, S., RABINOVITCH, R., and MCEACHERN, D. (1950). *J. Amer. med. Ass.*, **144**, 1353. 5 figs, 9 refs.

Cortisone was used in the treatment of twelve patients with muscular or neuromuscular disorders, thorough clinical, biochemical, and electromyographic investigation being carried out before, during, and after treatment. In all cases muscle biopsies were performed before cortisone was administered. Two typical cases of dystrophia myotonica were completely free of myotonia while they were having cortisone, this abnormality returning when cortisone therapy was stopped; there was also some increase of muscle power during treatment. Two patients with motor neurone disease showed no improvement with cortisone, while one patient with myasthenia gravis (apparently associated with a tumour of the thymus) became very much more myasthenic while he was having cortisone: when administration was stopped his condition gradually returned to its previous state. Of two patients with disseminated lupus erythematosus and marked muscle weakness both constitutional symptoms and muscle power improved with cortisone in one case, while in the other there was no increase of muscle power in spite of relief of the constitutional symptoms. One patient had an unusual type of muscular dystrophy with flexion contractures of the elbows and knees and fixation of the spine in hyperextension: no improvement occurred in this man. The remaining four patients suffered from a condition which the authors call " menopausal myopathy " in which, during the 50-60 age period, weakness of the muscles of the shoulder and pelvic girdles develops, with comparatively little wasting but with histological changes typical of a myopathy. In three of these patients there was considerable increase of power during cortisone administration and relapse when it was withdrawn. The authors have previously noted improvement in this condition when wheat germ oil is given and relapse when it is discontinued, and they raise the question as to whether " wheat germ may not contain building blocks for steroid hormones ". *J. W. Aldren Turner.*

Effects of ACTH in Patients with Mental Disease. ALTSCHULE, M. D., PROMISEL, E., PARKHURST, B. H., and GRUNEBAUM, H. (1950). *Arch. Neurol. Psychiat., Chicago*, **64**, 641. 6 figs, 17 refs.

This investigation was prompted by the work of Pincus and Hoagland, which suggests that in schizophrenia the adrenal cortex does not respond normally to stimulation by adrenocorticotrophic hormone (ACTH), and that of Gildea and others, which suggests that the response is normal.

The effects of ACTH on adrenal cortical function, as measured by eosinophil counts, the urinary uric acid: creatinine ratio, 17-ketosteroid excretion, and sweat sodium concentration, was the same in psychotic patients as in normal persons. When, however, 100 g. dextrose was given 1 hour after a single injection of 25 mg. ACTH, there was a greater rise in the blood sugar level over a 3-hour period in psychotics than in normal persons. (It is admitted that the numbers studied were so small that chance may have dictated the difference found in the two groups.)

It is known that large doses of ACTH or cortisone may give rise to mental changes in persons previously normal

mentally. The authors report two cases, both patients being manic depressives, in which the condition deteriorated after administration, in one case of 570 mg. ACTH in 17 days, and in the other of 900 mg. in 10 days. The history is also recorded of five patients previously given insulin or electric convulsion therapy who showed evidence of lessened responsiveness to ACTH.

It is suggested, therefore, [on rather dubious evidence] that psychotic patients show exaggerated metabolic changes after administration of ACTH, and that it might be possible to relate psychosis to metabolic changes consequent on an unusual response of the adrenal cortex to ACTH, or of other tissues to cortical hormone released during ordinary stress. *W. V. Wadsworth.*

Enhancing Effect of Cortisone upon Poliomyelitis Infection (Strain MEF1) in Hamsters and Mice. SHWARTZMAN, G. (1950). *Proc. Soc. exp. Biol., N.Y.*, **75**, 835. 13 refs.

Intramuscular doses of adrenocorticotrophic hormone (ACTH) and/or cortisone (5 mg. of each) were given to male Swiss mice weighing 10 to 14 g., and to male hamsters weighing 22 to 27 g., in groups of nine to 21 animals. The virus was maintained by serial intracerebral passage in mice and its identity checked periodically by neutralization tests with anti-Lansing monkey serum. The intracerebral inoculation dose for both animal species was 0·05 ml. of the brain emulsion, suitably diluted with saline. All surviving animals were examined daily for a period of one month.

Intracerebral inoculation of the virus in mice given cortisone and ACTH 2 hours previously was followed by a shortening of the incubation period and correspondingly earlier mortality compared with the controls. Intraperitoneal injection of the virus did not produce this effect.

In hamsters the effect was more striking. Previous experiments showed that these animals were normally quite resistant to intracerebral inoculation of poliomyelitis virus. After pretreatment with cortisone or ACTH and cortisone, what is normally a mild infection with small mortality rate became a rapidly progressing, violent, and uniformly fatal disease. ACTH alone failed to produce this effect, possibly, the author suggests, because of the elaboration of an unknown factor capable of reversing the enhancing effect of cortisone.

Norval Taylor.

Antagonism of Adrenocortical Extract and Cortisone to Desoxycorticosterone: Brain Excitability in Adrenalectomized Rats. WOODBURY, D. M., EMMETT, J. W., HINCKLEY, G. V., JACKSON, N. R., NEWTON, J. D., BATEMAN, J. H., GOODMAN, L. S., and SAYERS, G. (1951). *Proc. Soc. exp. Biol., N.Y.*, **76**, 65. 2 figs, 7 refs.

It has been shown that adrenal cortical extract (ACE) and cortisone will counteract the depressive effect of deoxycortone acetate (DCA) on brain excitability in intact rats. The present report concerns the effects of ACE and cortisone on adrenalectomized rats after implantation of DCA. Adult male Sprague-Dawley rats were used and the " electroshock threshold " (EST) was determined by the technique described by Davenport (*Amer. J. Physiol.*, 1949, **156**, 322). Some of the rats were then subjected to adrenalectomy and six 15-mg. pellets of DCA was implanted, some were left intact but DCA was implanted, and some served as untreated controls. The EST of the intact DCA-implanted rats increased in comparison with that of the controls, and that of the adrenalectomized DCA-implanted animals increased even more markedly. Both ACE and cortisone reduced the elevated EST of the adrenalectomized DCA-implanted rats; the degree of reduction was not, however, related to the loss of body weight. On withdrawal of the hormones the EST slowly increased to its original level.

These observations support the theory that DCA acts by antagonizing cortisone-like steroids at their site of action rather than by inhibiting pituitary release of adrenocorticotrophin (ACTH), since in the adrenalectomized animals the endogenous secretion of cortical steroids was *nil*. The authors suggest that the chemically similar DCA and cortisone compete for the same strategic loci in the cell. The test animals responded more rapidly to cortisone and ACE treatment if given water to drink instead of sodium chloride solution, suggesting a relationship between EST and the extracellular sodium level.

The possibility that brain excitability determinations may be useful as a method of assaying cortisone-like compounds is being explored. *Nancy Gough.*

Influence of Adrenaline and Insulin on Adrenal Cortical Response to ACTH. FORTIER, C., SKELTON, F. R., and CONSTANTINIDES, P. (1951). *Proc. Soc. exp. Biol., N.Y.*, **76**, 77. 8 refs.

It has been shown that ingestion of glucose enhances the response of hypophysectomized animals to adrenocorticotrophin (ACTH), suggesting that the blood sugar level affects the action of ACTH on the adrenal cortex. This paper records the results of a study of adrenal cortical response to ACTH in hypophysectomized male rats under conditions of adrenaline-induced hyperglycaemia and insulin-induced hypoglycaemia. Determinations of blood glucose, adrenal cholesterol and ascorbic acid, plasma ascorbic acid, and liver glycogen concentrations were made by standard methods. ACTH was injected subcutaneously, followed by adrenaline and insulin at intervals of 60 and 90 minutes respectively, so that the full action of ACTH coincided with the maximum hyper- and hypo-glycaemic levels. Hypophysectomized rats receiving ACTH, insulin, or adrenaline alone were killed at corresponding time intervals for comparison.

Changes in blood sugar level induced by insulin or adrenaline were not influenced by ACTH administration. Moreover, neither adrenaline nor insulin modified the effect of ACTH on the liver glycogen and adrenal cholesterol and ascorbic acid levels. Hence hyperglycaemia *per se* does not enhance the action of ACTH on the adrenal cortex; the effect of alimentary hyperglycaemia must be attributed to an increase in the total store of carbohydrates or to an excess production of intermediary metabolites. *Nancy Gough.*

Adrenal Cortical Failure Following Treatment with Cortisone and ACTH. Report of a Case. PROCTOR, E. L., and RAWSON, A. J. (1951). *Amer. J. clin. Path.*, **21**, 158. 2 figs, 6 refs.

This is believed to be the first case report of irreversible damage to the fascicular zone of the adrenal cortex following treatment with cortisone and ACTH.

The patient was a negress aged 36 who had had lupus

erythematosus and chronic cervicitis for 2 years. She was treated with radium for the cervicitis, but became progressively worse, with fever, malaise, weakness, and joint pains. She developed dry, scaly, depigmented areas on the nose, cheeks, and elsewhere, and there was stiffness and atrophy of the interosseous tissues of the hands and feet. All joints were painful on motion. The clinical diagnosis was lupus erythematosus disseminatus.

Cortisone was given in doses of 300 mg. on the first day, 200 mg. on the second day, and 100 mg. daily thereafter for 7 days. Soon after the start of treatment she felt much better and the joint pains had gone. A second course of cortisone was given, but pneumonitis developed and the patient died some 3 weeks later.

At necropsy the main findings were in the adrenal cortex. The cells of the zona fasciculata showed pyknosis of their nuclei and the cytoplasm was largely absent. As the lesions of lupus erythematosus disseminata were relatively inconspicuous in comparison with the marked damage to the adrenal cortex, it was presumed that adrenal cortical failure was the cause of death. *R. B. Lucas.*

Role of Cortisone in Regulation of Inflammation. DOUGHERTY, T. F., and SCHNEEBELI, G. L. (1950). *Proc. Soc. exp. Biol., N.Y.*, **75**, 854. 4 figs, 21 refs.

The authors describe their investigations into the histology of experimentally induced allergic and traumatic inflammation in adrenalectomized and adrenalectomized and cortisone-treated mice. Adrenal cortical secretions and exogenous cortisone were shown to inhibit inflammation without interfering with the antibody-antigen reaction. [As this paper is not readily abstracted, the original should be consulted for the technical details.] *Norval Taylor.*

Clinical Experiences with ACTH-treatment of Certain Skin Diseases. [In English.] BRODTHAGEN, H., REYMANN, F., and SCHWARTZ, M. (1951). *Acta endocrinol., Kbh.*, **6**, 110. 9 figs, 20 refs.

ACTH had no beneficial effect when given to a patient suffering from periarteritis nodosa and to four patients with severe psoriasis. Remarkable improvement in a man of 49 suffering from pemphigus was maintained 3 months after cessation of treatment, but a similar case in a female patient of 68 relapsed whenever the ACTH was withdrawn. There was marked improvement in one patient with diffuse sclerodermia, but no improvement in a second case. Small doses (5 to 45 mg. daily) were given, and it is advised that the treatment should be withdrawn gradually. No serious side-effects were seen, but most patients complained of tiredness and apathy on withdrawal of the drug. *John T. Ingram.*

Pituitary Adrenocorticotropic Hormone (ACTH) and Cortisone in Diseases of the Skin. I. Pemphigus Vulgaris and Other Bullous Dermatoses. CANNON, A. B., HOPKINS, J. G., ANDREWS, G. C., COLFER, H. F., GROSS, P., NELSON, C. T., and HOWELL, C. M. (1951). *J. Amer. med. Ass.*, **145**, 201. 6 figs, 10 refs.

The authors list nine skin conditions in which, according to published reports, pituitary adrenocorticotrophic hormone (ACTH) may be beneficial, and seven in which it appears to be ineffective or even detrimental. In the present paper they report the effects of ACTH treatment in eleven cases of bulbous dermatosis of various types seen at the Columbia-Presbyterian Medical Center, New York.

In five cases of pemphigus vulgaris, ACTH therapy was initiated after the disease had been present for periods ranging from one week in one case to one year in another. The first course usually consisted of from 60 to 100 mg. daily for 3 to 20 days, and in every case produced a remission, which was sometimes dramatic; but relapses always occurred on withdrawing the ACTH and the condition responded less well and only to greatly increased dosage in subsequent courses until finally new lesions appeared in spite of continued therapy. One of these patients died of fulminating pemphigus and another of mesenteric thrombosis, which was possibly due to co-existing Buerger's disease or to the effect of ACTH itself.

Two patients with pemphigus vegetans were also treated, both patients undergoing great clinical improvement and being discharged on a maintenance dose of about 100 mg. ACTH a day; one of them has actually returned to work. Of two cases of erythema multiforme pemphigoides, temporary clinical cure was obtained in one with an 11-day course of 100 mg. ACTH daily, followed after 6 months by a course of weekly injections of 50 mg. cortisone acetate. The other patient, after initial improvement on a dose of 80 mg. ACTH daily, decreasing to 40 mg. daily, relapsed 5 weeks after stopping the treatment, but again responded well to 40 mg. ACTH daily for 14 days. He has since been lost sight of. (In these two cases there was some difference of opinion concerning the diagnosis.) Two patients with epidermolysis bullosa of the congenital dystrophic type showed no objective improvement on treatment with cortisone acetate although appetite and sense of well-being improved.

In all eleven cases the blood pressure was initially low (96 to 108 mm. Hg systolic) but rose to normal levels on treatment. The frequent association with pemphigus of degenerative or necrotic lesions of the adrenal cortex and disturbances of serum electrolyte content is pointed out, although only in four of the present series was any abnormality of the blood chemistry, in the form of slightly diminished serum sodium content, found. ACTH and cortisone appear to produce identical effects, namely, easier management of the case, restoration of serum electrolyte balance, improvement of systolic blood-pressure and gain in weight. *Ferdinand Hillman.*

Role of Somatotrophic Hormone in the Production of Malignant Nephrosclerosis, Periarteritis Nodosa, and Hypertensive Disease. SELYE, H. (1951) *Brit. med. J.*, **1**, 263. 12 figs, 20 refs.

Female rats treated with electrophoretically pure somatotrophic hormone (STH) develop polyuria and hypertension with nephrosclerosis, myocarditis, and pancreatic polyarteritis nodosa. The liability of the animals to these toxic effects is augmented by unilateral nephrectomy and an excessive intake of sodium chloride. The toxic effects are similar to those produced previously by treatment with high doses of deoxycortone acetate (DCA) or a mixed anterior pituitary hormone preparation (LAP) which is rich in growth factor. They can be prevented by giving cortisone simultaneously in big enough doses to produce adrenal cortical atrophy. STH also increases the liability of rats to experimental

arthritis, while simultaneous administration of cortisone inhibits it, but larger doses of cortisone are required to prevent arthritis in STH-treated than in untreated rats.

It is suggested that STH stimulates the production of mineralo-corticoids like DCA by the adrenal cortex and also sensitizes the peripheral tissues to DCA-like substances. STH appears to be as important as ACTH in the production of the " diseases of adaptation ". It is responsible for the activity of the mineralocorticoids which stimulate defensive granuloma formation, while ACTH is responsible for the activity of the gluco-corticoids which inhibit such defensive mechanisms.

A. C. Crooke.

The Affective Response of a Patient with Chronic Ulcerative Colitis to Cortisone. McKELL, T. E., TUTHILL, S. W., and SULLIVAN, A. J. (1951). *Gastroenterology*, **17**, 20. 13 refs.

In a 35-year-old married woman who was " an example of a typical personality type " such as has been described in patients with chronic ulcerative colitis, the colitis, pyrexia, and general condition steadily worsened in spite of intensive therapy, including the administration of antibiotics. Upon the administration of cortisone, in doses of 100 mg. every 8 hours on the first day, 100 mg. every 12 hours on the second day, and 100 mg. daily for the next 10 days, a striking improvement in " responsiveness, affect, and mood " was observed as from the third day; this was followed, as from the eighth day, by satisfactory improvement in the diarrhoea, pyrexia, and vital signs and proctoscopic appearance of the colon. Improvement was maintained after the cortisone was discontinued, and the remission was still complete after 6 months.

The point of this report is that " the beneficial response was first manifested in the personality ". [It should be noted, however, that " the possibility of a miraculous remission was suggested to the patient " before treatment.]

Joseph Parness.

The Effect of ACTH on Nonspecific Ulcerative Colitis. ROSSMILLER, H. R., BROWN, C. H., and ECKER, J. A. (1951). *Gastroenterology*, **17**, 25. 1 fig., 4 refs.

In five patients suffering from diarrhoea, pyrexia, and the usual toxic manifestations of an acute exacerbation of chronic ulcerative colitis the usual measures, including the administration of antibiotics, had given no response. Upon the administration of ACTH in doses of 25 mg. every 6 hours for 10 days a fall in temperature to normal occurred in three patients, but without improvement in diarrhoea or in the appearance of the rectal mucosa; in one case the subsidence of the temperature to normal was accompanied by improvement in the diarrhoea and in the appearance of the rectal mucosa; in one patient (who had a low-grade pyrexia) there was no reduction of temperature, nor was there improvement in diarrhoea or in appearance of rectal mucosa.

ACTH appears to be effective in reducing the febrile reaction in acute toxic ulcerative colitis. *Joseph Parness.*

Physiological Reaction to Pituitary Adrenocorticotropic Hormone (ACTH) in Severe Burns. WHITELAW, M. J. (1951). *J. Amer. med. Ass.*, **145**, 85. 4 figs, 12 refs.

Evidence is accumulating that adequate physiological adrenal cortical stimulation with ACTH should inhibit or reverse all the physiological phenomena produced by sudden severe stimuli. When this does not happen, the author suggests, the normal response is not sufficient in relation to the intensity of the stimulus. Extensive burns which, if involving over 60 per cent. of the body surface, are usually fatal, provide such a stimulus.

To test this theory a case of petrol burns involving over 70 per cent. of the body surface was treated, after 24 hours of the usual routine burns treatment, with ACTH alone, 20 mg. being given 6-hourly intramuscularly; this was gradually reduced to 10 mg. 6-hourly by the 32nd day and was continued at this dosage until the 92nd day, when it was discontinued. On this treatment the patient improved rapidly, showing minimal signs of toxicity and prostration and experiencing very little pain. Kidney function increased early and chloride excretion remained low. Haemoconcentration did not occur, and the anaemia which was present was attributable in part to haemodilution. Mild hypoproteinaemia was recorded. No fibroblastic proliferation was noted, and epithelization was rapid except in the areas of very severe third-degree burns. Here 29 out of thirty homologous pinch grafts from two donors took when applied on the 42nd day, and epithalization was complete by the 101st day. Some fibroblastic proliferation occurred after cessation of the drug and melanin deposits were extremely intense, especially at the belt line.

The author considers that the tremendous saving both in expense and personnel calls for a re-evaluation of present methods of treating such patients, and that the success of pinch grafting may open up new fields in transplantation and plastic surgery. *A. Ackroyd.*

The Influence of Cortisone on Skin and Wound Healing in Experimental Animals. BAXTER, H., SCHILLER, C., WHITESIDE, J., and STRAITH, R. E. (1951). *Plast. reconstr. Surg.*, **7**, 24. 6 figs, 7 refs.

The authors review the literature and give an account of their own experiments on three rabbits. Previous workers have shown that in rabbits and mice ACTH or cortisone retards the growth of all elements of connective tissue, as well as the growth of granulation tissue in open wounds and in fractures. These effects are not blocked by ascorbic acid. After cortisone injection there was no change in the macroscopical appearance of healing, sutured skin incisions in rabbits, compared with similarly sutured incisions made in the same animals and allowed to heal before injections of cortisone were started.

Microscopical specimens (haematoxylin-eosin and Weigert elastin stains) showed marked differences in wound healing in the cortisone-injected series. In fibroblastic proliferation, growth of capillary vessels, and union by epithelium they lagged behind the controls. There was a greater tendency to haemorrhage into the wounds, and atrophic changes of the skin remote from the wounds were demonstrated.

A possible clinical application—the use of cortisone to prevent the overgrowth of fibrous and granulation tissue and keloid formation—is mentioned.

W. Skyrme Rees.

Treatment of Nephrosis with Cortisone. LEUTSCHER, J. A., and DEMING, Q. B. (1950). *J. clin. Invest.*, **31**, 1576. 5 figs, 21 refs.

In studying the effect of cortisone on the various manifestations of the nephrotic syndrome in eleven patients at Stanford University School of Medicine,

San Francisco, the sodium-retaining activity of the urinary corticoids, which is increased in the nephrotic syndrome, was measured by biopsy in adrenalectomized rats by comparison with the effect of a standard dose of deoxycortone acetate. As might be expected, during cortisone administration (100 to 300 mg. a day for 5 to 16 days) some manifestations of the renal upset were made worse. Albuminuria and oedema tended to increase, sodium excretion diminished, and the serum protein level rose a little. In two cases a rise in serum potassium level prevented the completion of treatment. When cortisone was stopped, however, diuresis occurred, in six patients, with loss of all oedema. This improvement lasted from a few days to several months, usually starting 3 days after cortisone was stopped. There was also a reduction in the albuminuria and excretion of sodium-retaining corticoids. Creatinine excretion increased, as did the serum sodium level. There was no alteration in serum cholesterol level, haematocrit, or erythrocyte sedimentation rate. [The blood urea level is not mentioned.] The value of cortisone is thus apparent only after its withdrawal, during the time when endogenous adrenal activity is depressed. Experimentally, adrenalectomy will reduce albuminuria, and intercurrent infection is known to bring about clinical improvement in cases of wet nephritis. The other five patients were not improved, but the subsequent improvement of four of them following intravenous albumin therapy is reported, and these two forms of treatment may be complementary. The authors point out that the fundamental disorder in this disease still appears to lie in the kidney. *K. Gurling.*

Results of Cortisone Treatment in Dublin. MOORE, H. L., JESSOP, W. J. E., and O'DONOVAN, D. K. (1951). *Irish J. med. Sci.*, **6**, 95. 1 fig., 1 tab.

A preliminary report on the results of treatment with the first supplies of cortisone used in Dublin, including an account of the effects of the drug in both ocular and general disease. In the ocular cases, subconjunctival injection of 1·25 mg. at 5- to 6-day intervals was the usual dosage, although the effects of systemic administration were observed in some cases. Statistics are not given, but it is stated that scleritis associated with severe arthritis has been seen to clear rapidly with systemic treatment, that keratitis, and particularly interstitial keratitis, has responded well, and that the cleaning of corneal opacities due to chemical burns has appeared to be accelerated. Absorption of keratic precipitates and clearing of the vitreous, with improvement of vision in iridocyclitis is also reported. *H. E. Hobbs.*

Cortisone in the Treatment of Phlyctenular Kerato-conjunctivitis. THYGESON, P., and FRITZ, M. H. (1951). *Amer. J. Ophthal.*, **34**, 357. 1 tab., 2 refs.

The results of cortisone therapy in fourteen cases of phlyctenular kerato-conjunctivitis are described. In twelve of them dramatic resolution of the phlycten with whitening of the eyes was seen within 48 hours of treatment being begun. The remaining two cases, in which the exacerbation was of long duration, responded in four and six days respectively. In one instance of a minimal lesion, a single drop (of a 1 in 2 dilution of cortisone acetate) was sufficient, in three others, seen during the first attack, a single subconjunctival injection of 0·1 ml. was employed, and for the remaining (recurrent) lesions drops were instilled hourly for two days and q.i.d. for a short period. Similar results in eleven of a further twelve cases treated later are mentioned. *H. E. Hobbs.*

Cortisone in Treating Stevens-Johnson Syndrome. BLEIER, A., and SCHWARTZ, E. (1951). *Amer. J. Ophthal.*, **34**, 618. 7 refs.

The report of a case which presented with severe bilateral conjunctivitis, ulcerative stomatitis, and balanitis, accompanied by pyrexia and a dry cough. Initial treatment with aeureomycin (250 mg. 4-hourly, orally, and a mouth wash containing 40 mg. per ml.) was followed by gradual improvement of the general condition, but the ocular and oral conditions persisted a week later and bullous cutaneous eruptions had appeared.

Parenteral cortisone (600 mg. in 3 days) produced a dramatic response within 24 hours, and no recurrence was seen during the succeeding 4 months. *H. E. Hobbs.*

Interstitial Keratitis treated with Cortisone. GEDDES, A. K., and MCCALL, M. F. (1950). *Canad. med. Ass. J.*, **63**, 601. 4 refs.

An interstitial keratitis of five weeks' duration, in a 10-year-old girl, responded poorly to systemic penicillin. Then cortisone, 100 mg., was given daily. By the sixth day of treatment the corneae were clearing markedly; by the 14th day little haze was present. The old neglected lesion in the right eye cleared more completely than the fresh lesion in the left eye. There was no change in the blood Wassermann reaction. *C. McCulloch.*

ACTH and Cortisone in Ocular Inflammation, Parenteral and Local Use. ROME, S., KOFF, R., KASPER, R., BUTTON, R., COMMONS, R., and STARR, P. (1950). *Ann. west. Med. Surg.*, **4**, 799. 2 figs.

The chief value of ACTH or cortisone is to prevent an acute ocular inflammation from becoming chronic. The only cases of iritis that did not respond to cortisone were those in which the pupil was fixed and not dilatable. Intramuscular ACTH is effective in some cases of chronic granulomatous uveitis. Subconjunctival injection of cortisone is effective in acute iritis, chronic keratitis, and helpful in vernal catarrh. *I. E. Gaynon.*

Topical Cortisone in Eye Disease. JENSEN, C. D. F., and WARD, J. F. (1951). *Northw. Med., Seattle*, **50**, 36.

The authors used topical and subconjunctival therapy in a series of thirteen cases with anterior segment eye disease—eight of iritis, two of episcleritis, and one each of conjunctivitis and blepharitis. Drops were mainly used consisting of 25 mg. per ml. stock solution of cortisone acetate diluted with an equal amount of normal saline and they were administered hourly. The immediate results were excellent, the late results were not discussed. *S. J. H. Miller.*

Local Use of Cortisone in Ophthalmic Diseases. MOSHER, H. A. (1951). *Arch. Ophthal., Chicago*, **45**, 317. 3 tab., 2 refs.

The results of local cortisone treatment in a series of 53 patients are recorded. The author considers that cortisone administered in the form of drops is more effective than subconjunctival injection. *C. A. Cook.*

Physiological Effects of Cortisone and Pituitary Adreno-corticotropic Hormone (ACTH) in Man. SPRAGUE, R. G., POWER, M. H., and MASON, H. L. (1950). *J. Amer. med. Ass.*, **144**, 1341. 16 figs, 28 refs.

Some Observations on Treatment of Lupus Erythematosus Disseminatus and Spondylarthritis Ankylopoietica with ACTH and Cortisone. [In English.] HOLTEN, C. (1950). *Scand. J. clin. Lab. Invest.*, **2**, 300. 3 figs, 5 refs.

ACTH in the Treatment of Rheumatic Fever. RØJEL, J. (1951). *Acta endocrinol., Kbh.*, **6**, 221. 4 figs, 8 refs.

Clinical Experience with Adrenocorticotrophic Hormone (ACTH) in Rheumatoid Arthritis. (Klinische Erfahrungen mit dem adrenocorticotropen Hormon (ACTH) bei chronischer Polyarthritis.) KOTHÉ, W. (1951). *Med. Klinik*, **46**, 35. 25 refs.

Experience with Cortisone in the Treatment of Rheumatoid Arthritis. BILKA, P. J., and CADER, G. (1951). *Postgrad. Med.*, **9**, 231. 3 figs, 6 refs.

The Pituitary and the Osteopathies. (La hipofisis y las osteopatías.) MUCH, V. (1951). *Rev. oto-neuro-oftal.*, **26**, 17.

ACTH and Cortisone in Ophthalmology. (ACTH y cortisona en oftalmología.) PURCALLAS, E. (1950). *Galicia Clin.*, **22**, 679.

Other General Articles

Addison's Disease occurring in Two Brothers. BRIGGS, J. N., GOODWIN, J. F., and WILSON, A. (1951). *Brit. med. J.*, **1**, 115. 3 figs, 7 refs.

Addison's disease occurring during adolescence in two brothers, and the necropsy findings in one of them, are reported.

The first patient, a boy of 12, had typical clinical and biochemical signs which became normal on treatment with adrenal cortical extract, deoxycortone acetate, and salt. Associated endocrine changes—bilateral undescended testicles and an underdeveloped penis—were rectified following the administration of chorionic gonadotrophin. His brother, aged 17, was admitted within a year; although the only abnormality was buccal and generalized pigmentation, he suddenly deteriorated after the administration of intravenous saline and died in 3 days. At necropsy both suprarenal cortices showed simple atrophy; the thymus was grossly enlarged, and both lungs had supernumerary lobes.

There was no family history of Addison's disease. The authors consider that simple atrophy of the suprarenals was the cause of the disease in both brothers, although the younger one had lived on unboiled, unpasteurized farm milk all his life and had calcified abdominal lymph nodes; they point out that the occurrence of Addison's disease at so early an age and in siblings suggests a genetic basis.

The literature on the genetic factor in Addison's disease is briefly reviewed, but it is emphasized that most of the cases were inadequately documented. The present authors conclude that the evidence in favour of a genetic factor in Addison's disease is suggestive. *Helen Grant.*

Renal Rickets and Osteitis Fibrosa in Children and Adolescents. FOLLIS, R. H. (1950). *Bull. Johns Hopk. Hosp.*, **87**, 593. 16 figs, 12 refs.

The author records sixteen cases of renal insufficiency, due to various lesions, in which skeletal changes were discovered. Two main osseous lesions were seen: (1) bony trabeculae coated with osteoid and showing a resemblance to rickets, and (2) bony destruction with fibrous-tissue replacement suggestive of osteitis fibrosa. Whereas the youngest children showed changes of rickets only, older cases presented a mixed picture or one of osteitis fibrosa only. Stress is [rightly] laid on the fact that the bony lesions which may complicate renal disease are exceedingly complex, and that while excess parathormone may or may not play a part, it is quite erroneous to regard these lesions as purely secondary to hyperparathyroidism and therefore unrelated to true rickets. *G. J. Cunningham.*

Normal Values for Serum Cholesterol and Basal Metabolic Rates and their Correlation in Normal Man. PEELER, A. L., HEPLER, O. E., KINNEY, V. M., CISLER, L. E., and JUNG, F. T. (1950). *J. appl. Physiol.*, 3, 197. 1 fig., 18 refs.

The authors report an investigation into the possible relationship between the serum cholesterol content and basal metabolic rate (B.M.R.) which was carried out at North-western University Medical School, Chicago, on 72 healthy male students between 19 and 27 years old. The subjects were given a standardized supper and kept under a standard regimen during the evening before the tests, which were all carried out before breakfast. Two B.M.R. determinations were made with a Benedict-Roth apparatus, the average of two 6-minute runs being taken, followed by a blood serum cholesterol estimation, carried out in duplicate by a modified Bloor's method. The whole procedure was repeated after a 7-day interval with 32 of the subjects, and after an average of 38 days with the remaining forty. The mean B.M.R. for the whole group was 37·0 calories per square metre per hour (range, 30·9 to 45·3) and the test-retest correlation coefficient for the two successive sessions was +0·60. The mean serum cholesterol value was 189 mg. per 100 ml. (range 131 to 303) and the test-retest correlation coefficient at 7- and 38-day intervals was +0·87, indicating that Bloor's method was reliable and that the serum cholesterol level was a more stable characteristic of normal individuals than the basal metabolic rate. There was no correlation between the cholesterol value and the basal metabolic rate, as is shown by the statistically insignificant correlation coefficient of −0·03. *R. P. Hullin.*

Polyarthritis (Osteomyelitis) Variolosa. [In English.] WIERSEMA, J. S. (1950). *Arch. chir. neerl.*, **2**, 140. 14 figs, 9 refs.

During a recent smallpox epidemic in Djakarta some of the patients had affections of the joints. The author surveys the literature and reports the cases of three Indonesian children who had joint affection with smallpox: (1) Boy aged 21 months: left elbow swollen, radiographic changes in left elbow and right wrist, no puncture, Wassermann and Kahn reactions negative. (2) Girl aged 9 years: both elbows swollen, pus found but not investigated further, Wassermann and Kahn reactions strongly positive. (3) Girl aged 4 years: both elbows, both knees, right wrist, and left shoulder affected, pus found in elbows but not examined, Wassermann reaction negative and Kahn reaction ±.

[The diagnosis of polyarthritis variolosa is not proved. Although no exact figures are given there appear to have been something like seven cases with joint affections out of 2,500 smallpox cases, which rather indicates an intercurrent disease.] *J. Agerholm.*